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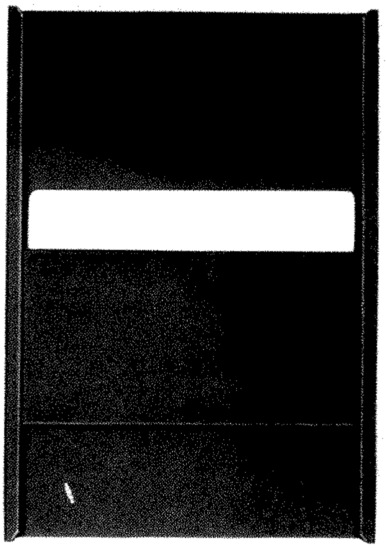

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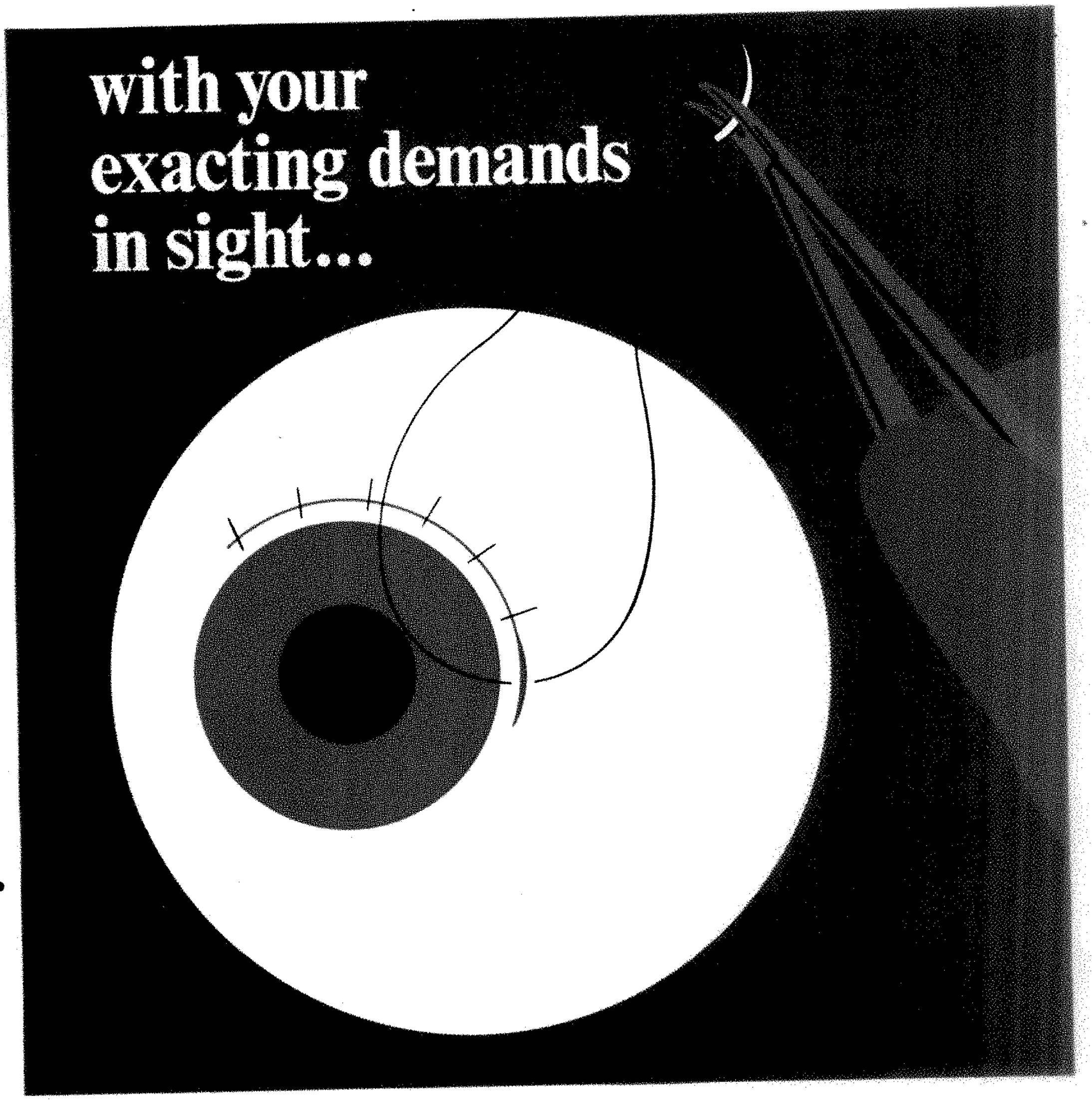

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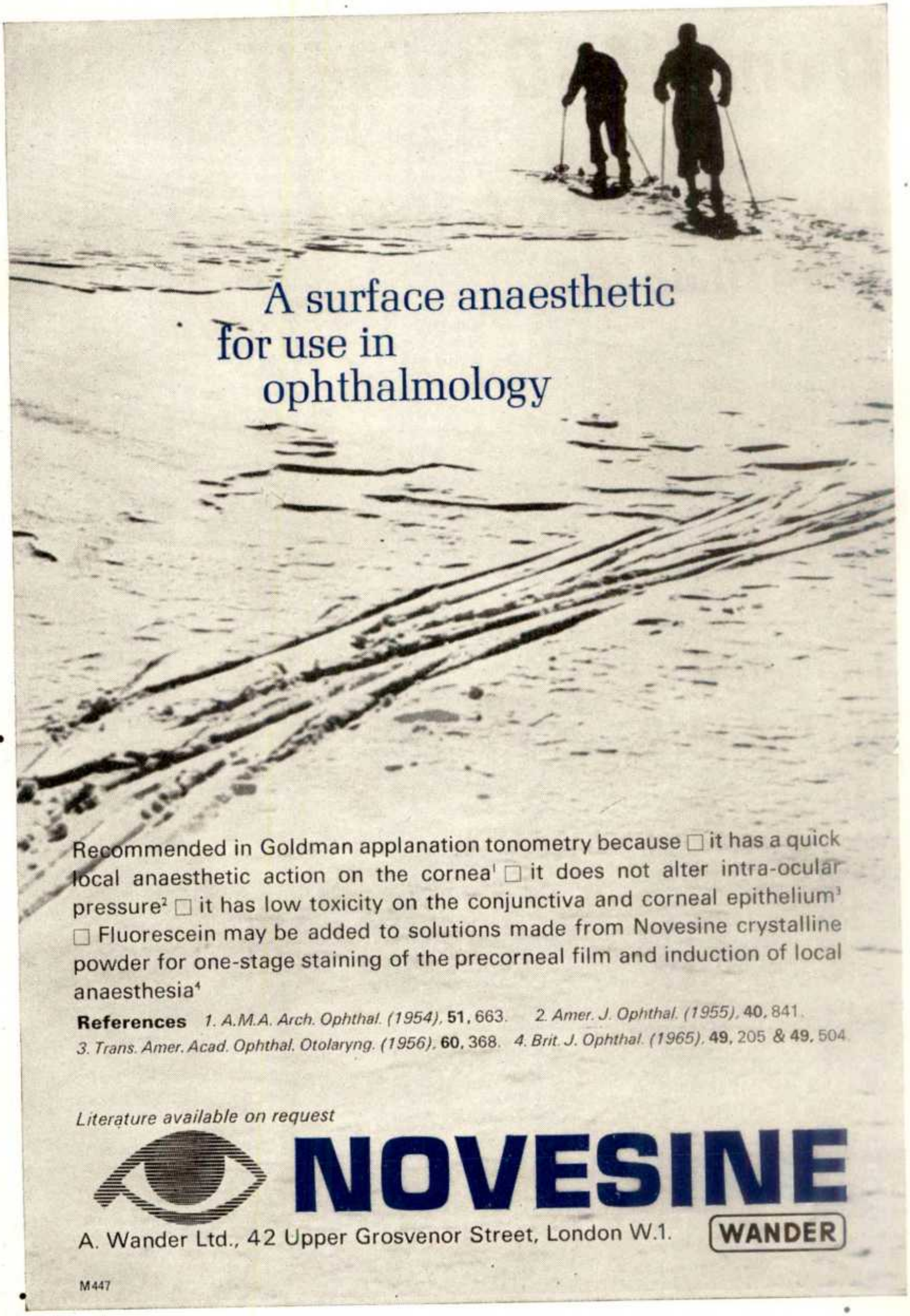

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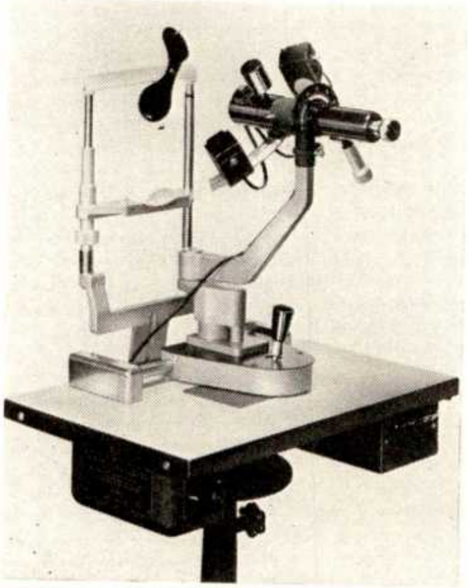

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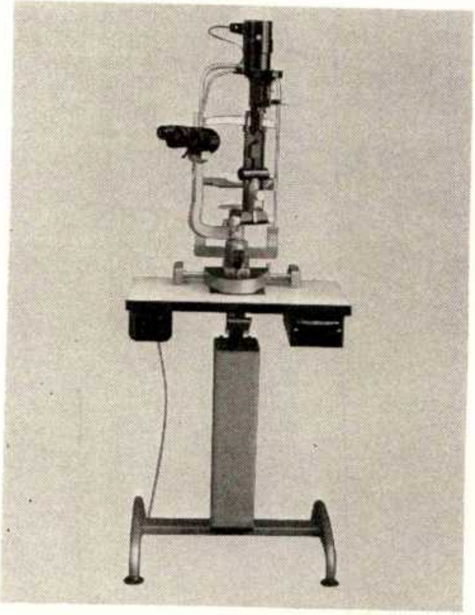

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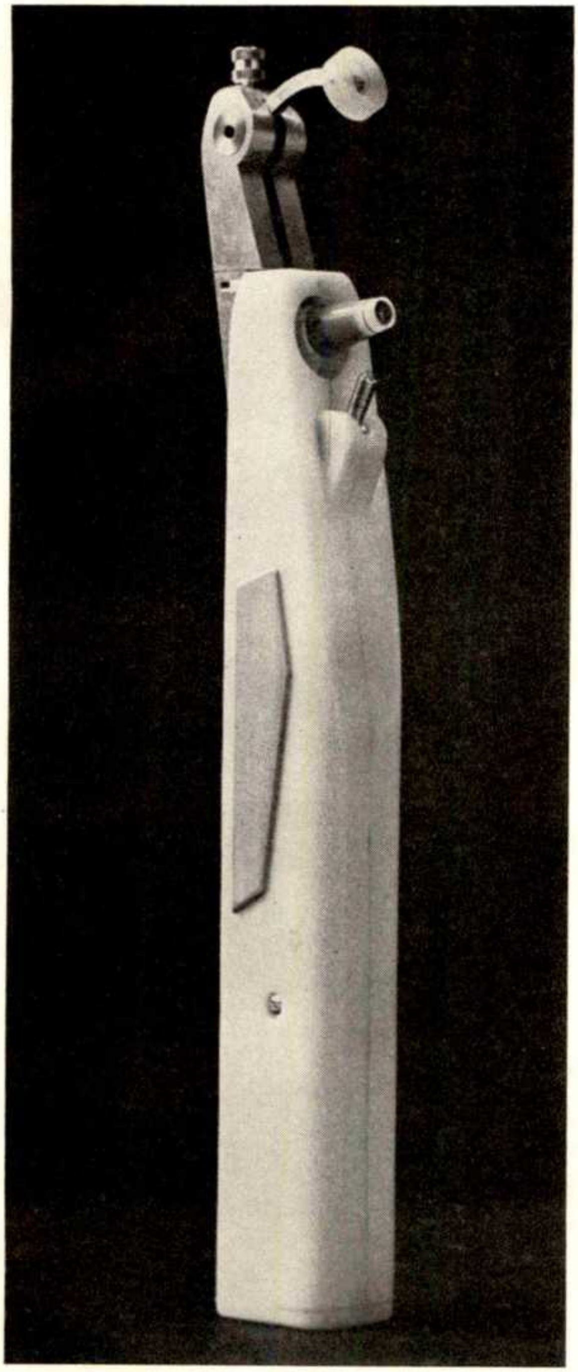

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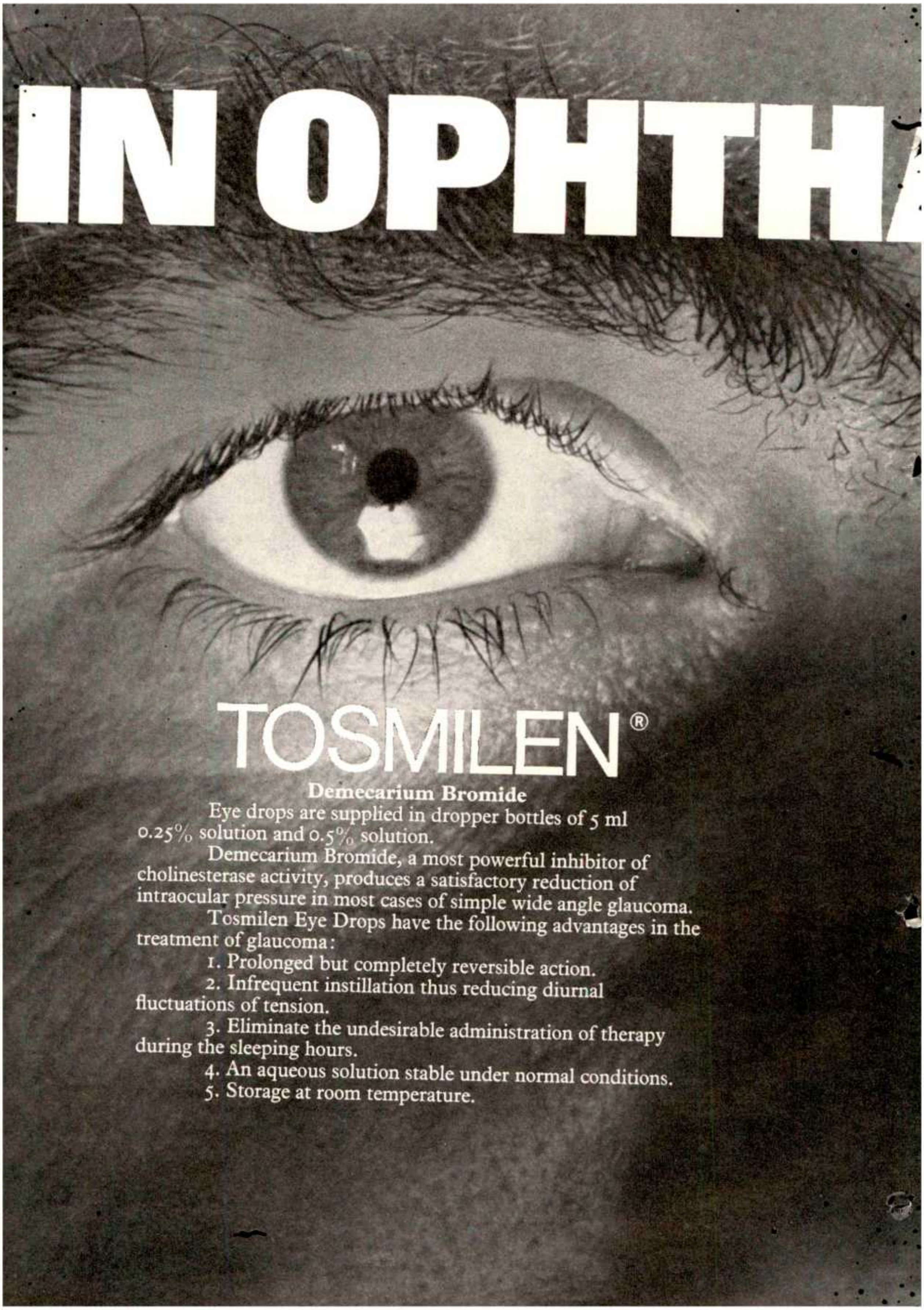

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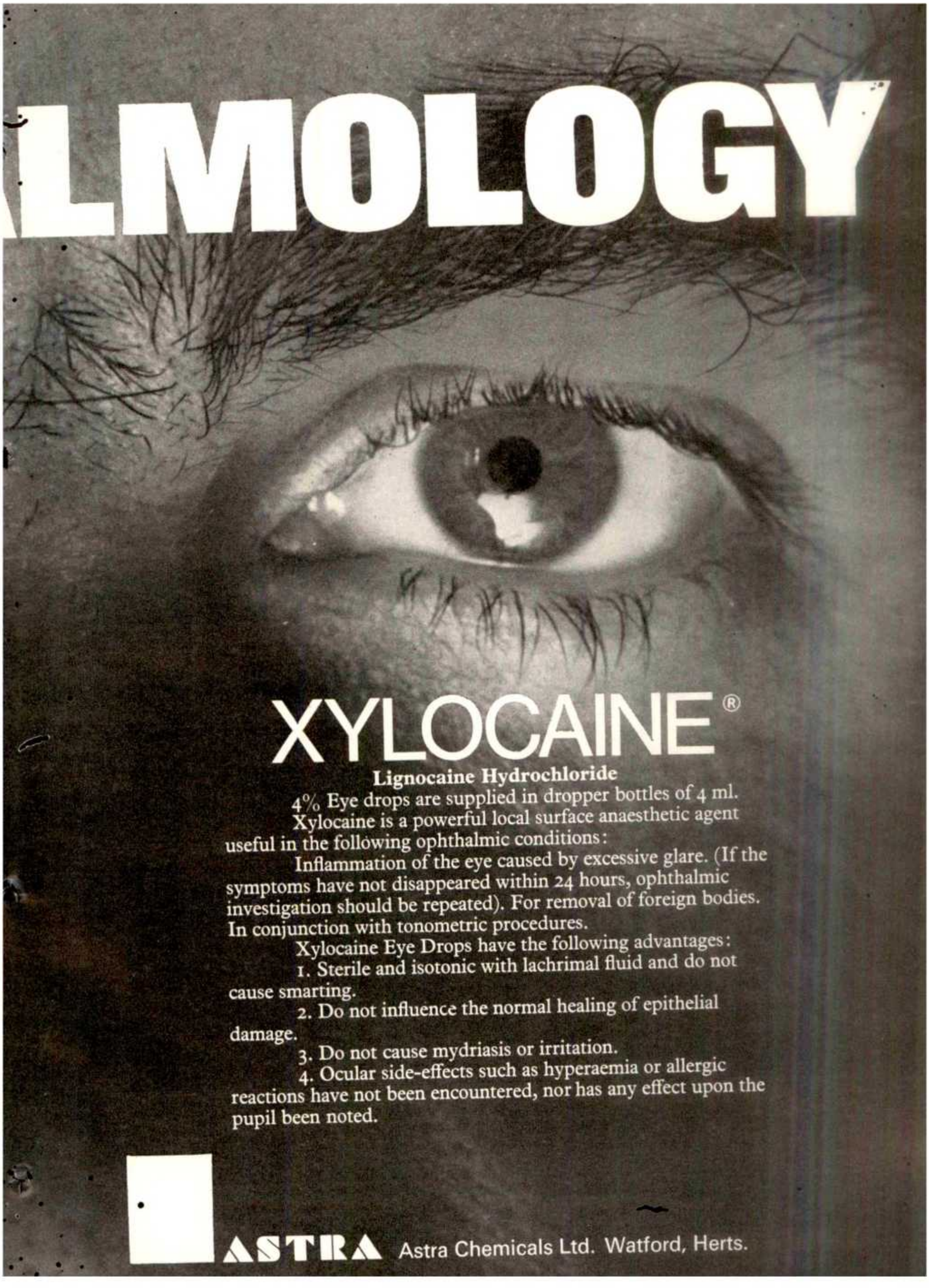

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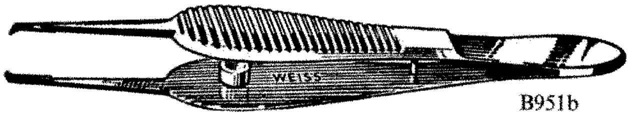

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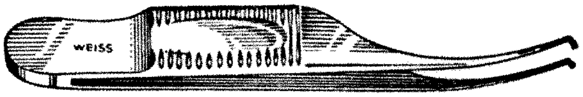

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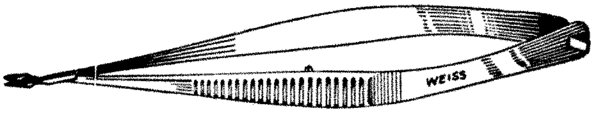

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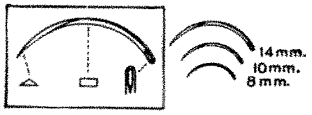

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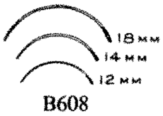

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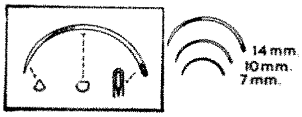

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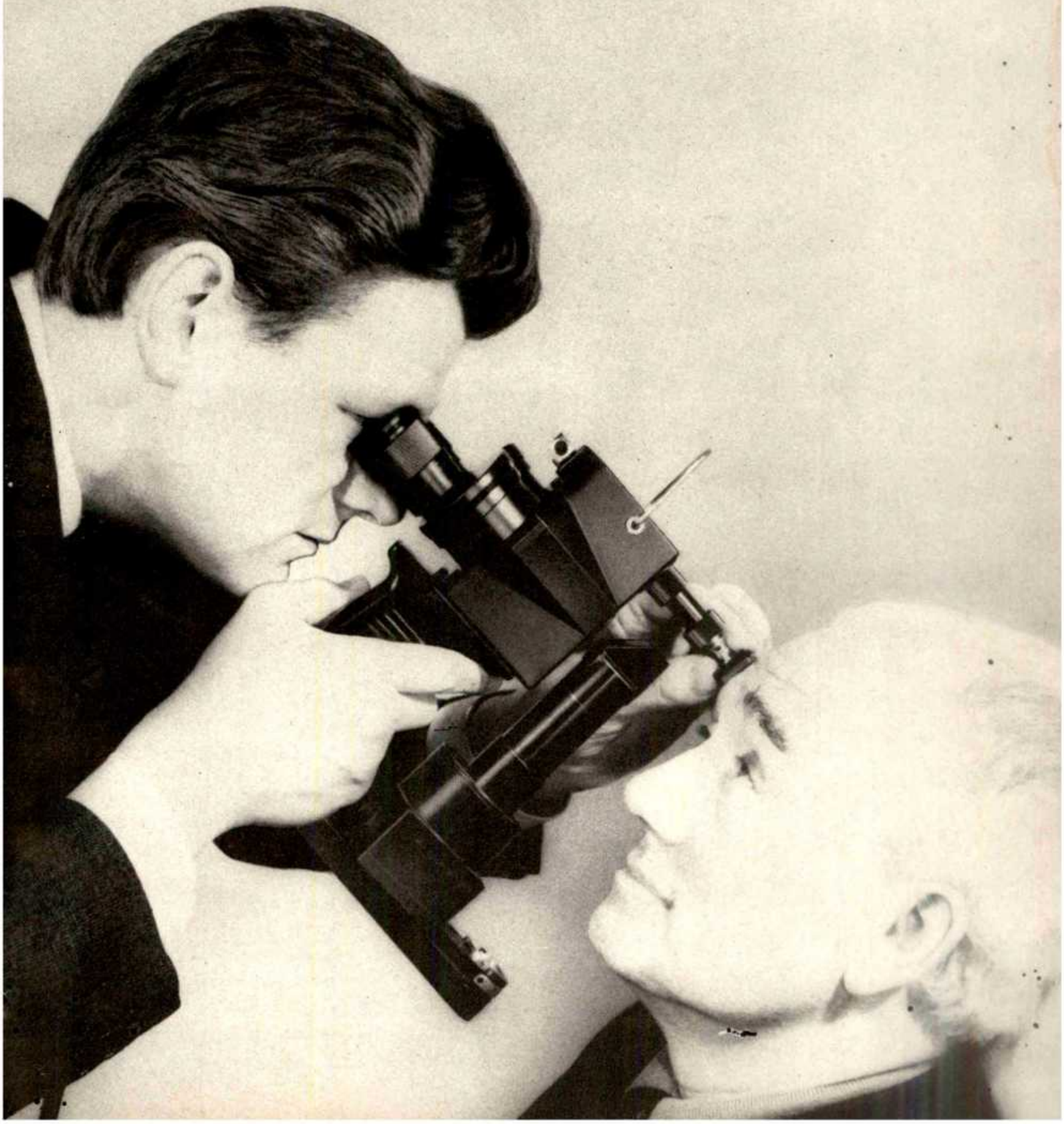

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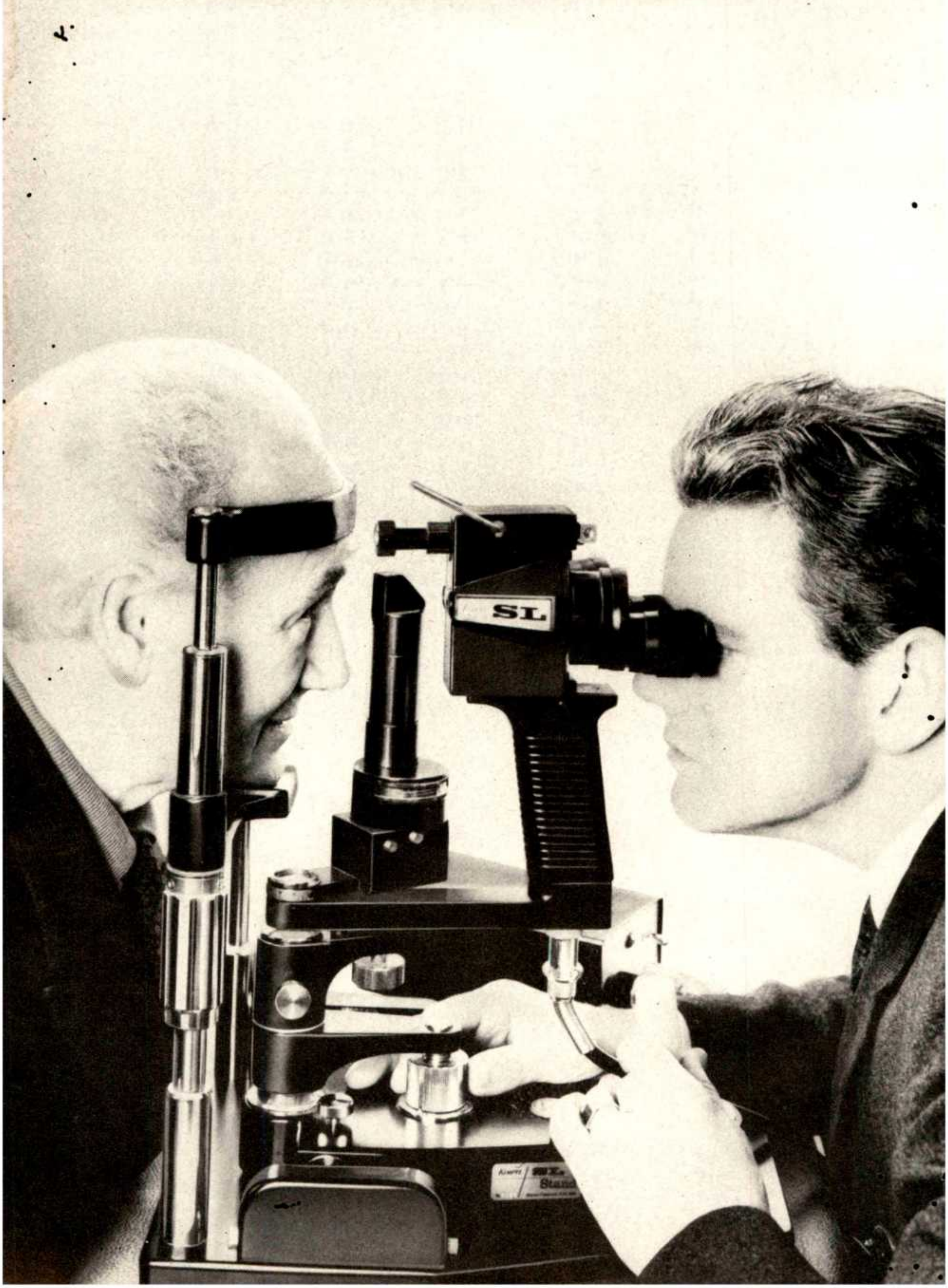

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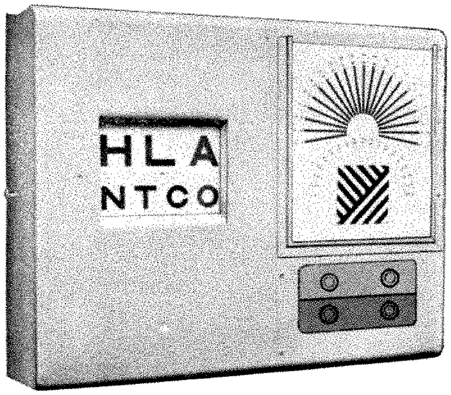

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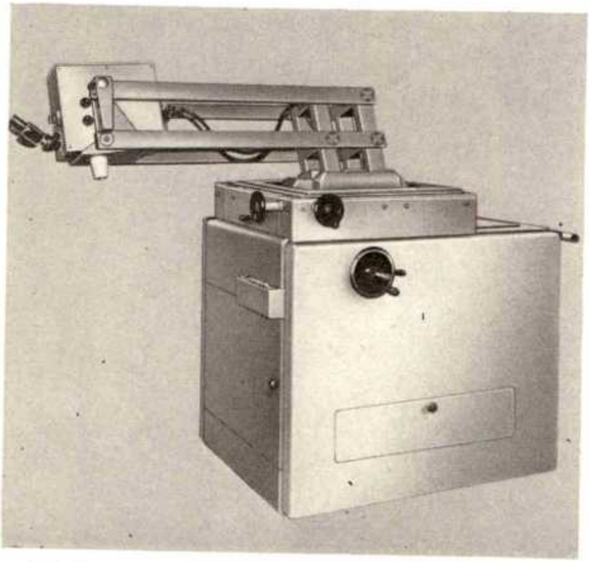

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UNIVERSI

Communications

Vaso-glial connections in the rabbit retina

BRENDA TRIPATHI AND NORMAN ASHTON

Department of Pathology, Institute of Ophthalmology, University of London

The anatomy and development of the retinal vasculature of the rabbit have been described by numerous workers in the past (His, 1880; Langenbacher, 1880; Bruns, 1882; Schultze, 1892; Fuchs, 1905; Eisler, 1930; Kuwabara and Cogan, 1960; Mutlu and Leopold, 1964; Agarwal, Singh, and Dayal, 1966). Particularly valuable accounts of recent years are those of Michaelson, 1954; Rohen, 1954; Hyvärinen, 1967. Although there has been considerable controversy, it is now generally agreed that the vessels are confined to the medullated nerve fibre layers, which extend horizontally as wing-shaped areas on either side of the disc, and, apart from ~~deep~~ capillary branches at the disc margin and deep loop capillaries arising from the inner two-thirds of the vascular complexes, it is thought that they lie entirely on the surface of the retina, upon or in close relation to the inner limiting membrane. Two modifications of this view were briefly referred to in recent papers: Rohen (1954) stated that the "larger branches of the vessels are connected by a few connective tissue fibres to the retina", and Hyvärinen (1967) illustrated what he believed to be a sheath of internal limiting membrane around a capillary. There appears, however, to be no previous account in the literature of the exact ultrastructural relationship of the vessels to the retina nor of the remarkable glial tufts which extend out of the retina, at frequent and irregular intervals, to embrace and anchor the superficial vessels to the retinal surface. We have recently observed these structures in an electron microscopical study of the rabbit retina and here present an account of our findings.

Methods and material

The eye of a young adult rabbit (13 weeks old) was enucleated under Nembutal anaesthesia and was fixed immediately by cutting open at the ora serrata in 1 per cent. isotonic osmium tetroxide solution at pH 7·4. The zone of the retinal vascular complex was dissected out and embedded in Araldite. Serial thick sections (1–2μ), perpendicular to the plane of the retina, were cut from the tip of the vascular complex to the optic disc and were stained with toluidine blue for light microscopy. Thin sections for electron microscopy were cut from selected areas of the block and stained with uranyl acetate and lead citrate. Sections were examined and the electron micrographs taken with an AEI EM6 electron microscope.

This communication is dedicated to Prof. Dr. Josef Böck on the occasion of his 70th birthday.

Received for publication October 29, 1970
Address for reprints: Department of Pathology, Institute of Ophthalmology, Judd St., London WC1H 9QS

Findings

LIGHT MICROSCOPY

In cross-sections the superficial vessels of the retinal vascular complex were found in three distinct locations:

(1) Lying free in the vitreous near to the retinal surface but having no contact with the internal limiting membrane (Fig. 1).

(2) Lying near to or upon the surface of the internal limiting membrane, and in places adhering to or enwrapped by glial protrusions or tufts extending towards them from the nerve fibre layer of the retina (Figs 1 and 2).

(3) Apparently lying just within the nerve fibre layer (Fig. 3).

ULTRASTRUCTURE

In the first group, illustrated in Fig. 4, the vessels are seen to possess a normal vascular architecture consisting of a lumen filled with plasma and blood corpuscles, an endothelial lining having tight junctions, and a tenuous basement membrane containing intramural pericytes (Ashton and Oliveira, 1966); larger vessels also show one or two layers of muscle cells. They lie free within the vitreous surrounded by a condensation of vitreous fibrils which fuse with their basement membranes. At higher magnifications the vitreous fibrils can be seen widely separating the cell membrane and basement membrane of the vessel from the basement membrane and plasma membrane of the glial cell, which together constitute the internal limiting membrane of the retina (Fig. 5). Occasionally vitreal cells are seen lying close to the vessels.

Vessels seen in sections of the second group show a similar structure, but their close approximation to the internal limiting membrane is now apparent. Occasionally, the vessels dip into the surface of the retina, their basement membranes lying in close contact with the internal limiting membrane which remains intact (Fig. 6). In other places, however, glial protrusions covered by internal limiting membrane extend into the vitreous to come in contact with the vessel wall (Fig. 7). At frequent but irregular intervals, sections show mushroom-like protrusions of glial tissue extending into the vitreous through narrow breaks in the internal limiting membrane, to enclasp and almost completely surround the vessel (Fig. 8), thus forming a firm adhesion to the retinal surface. These protruding glial cells sometimes possess basement membranes distinct from those of the vessels, but in other areas are devoid of basement membrane; their plasma membranes then abut directly onto vitreous or onto vascular basement membrane. The tufts show an internal structure comparable to the glial cells in the retina, with which their cytoplasm and intracellular fibrils are continuous (Figs 8 and 9). The latter are orientated in the long axis of the glial cells and are often condensed as they curve around the edge of the break in the internal limiting membrane (Fig. 10).

Sections of vessels in the third group, wherein vessels appear to lie within the inner nerve fibre layer, show at high magnification that they are not actually within the retina, but lie encupped in invaginations of the internal limiting membrane from which they are separated by a delicate layer of collagenous fibrils (Fig. 11).

Discussion

This electron microscopical study would seem to resolve completely the old controversy whether the superficial vessels of the rabbit retina lie within or upon the retinal surface.

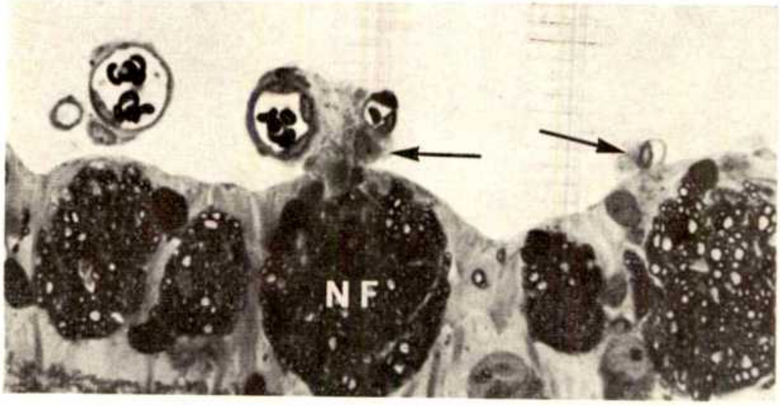

FIG. 1 *Cross-section of superficial retinal vessels and medullated nerve fibre layer (NF) of rabbit retina, showing vessels lying free in the vitreous (left) and others connected to the retina by glial tufts (arrows)* × 530

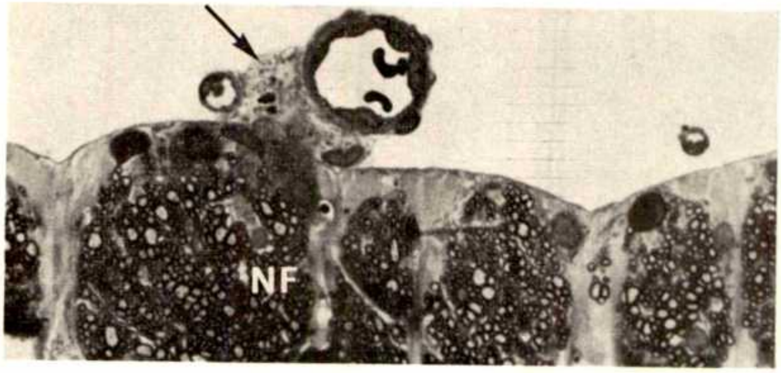

FIG. 2 *Centrally two retinal vessels are connected to the retina by a glial tuft (arrow). On the right a capillary lies free in the vitreous.* × 660

NF = Medullated nerve fibre layer

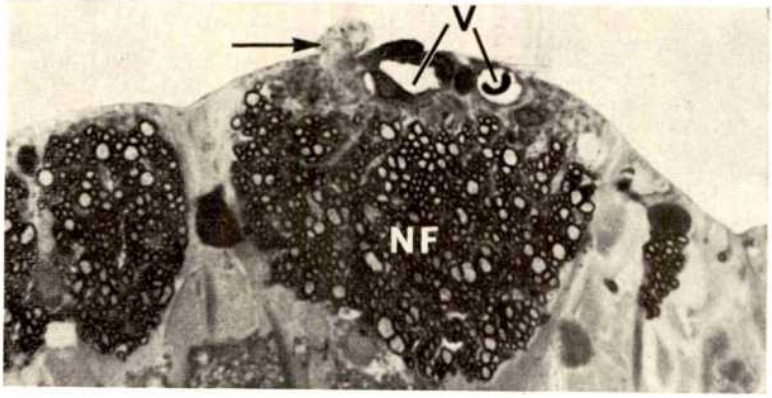

FIG. 3 *Cross-section of retina, showing vessels (V) apparently lying within the inner nerve fibre layer (NF). Note also a protruding glial tuft (arrow).* × 660

Footnote: Figs 1–3. Araldite sections. Toluidine blue stain

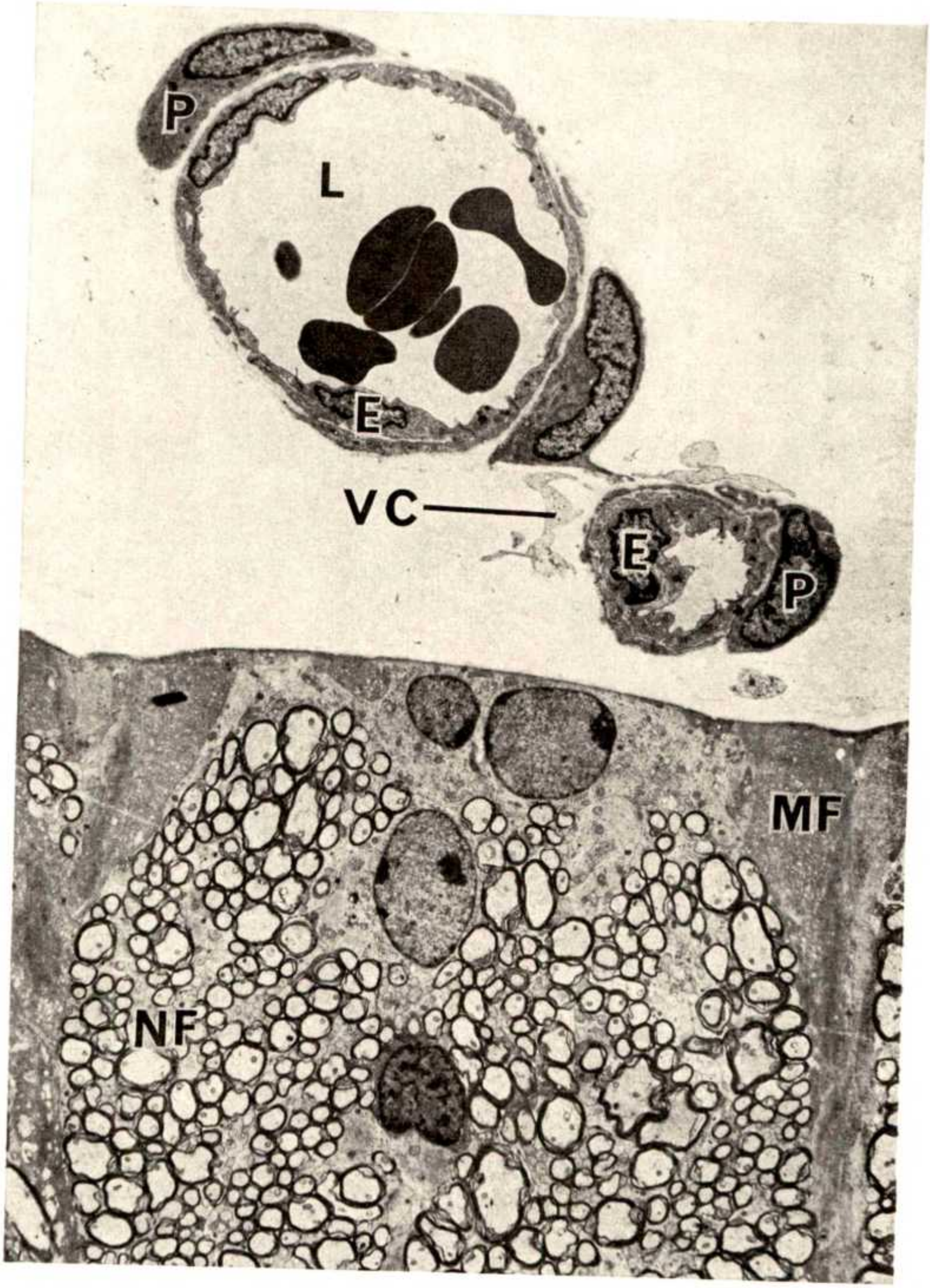

FIG. 4 *Electron micrograph, showing blood vessels lying free in the vitreous* × 3,250 (approx.)

L = lumen containing plasma and blood corpuscles

E = endothelium P = pericyte VC = vitreal cell

NF = nerve fibre layer of the retina MF = Müller fibres

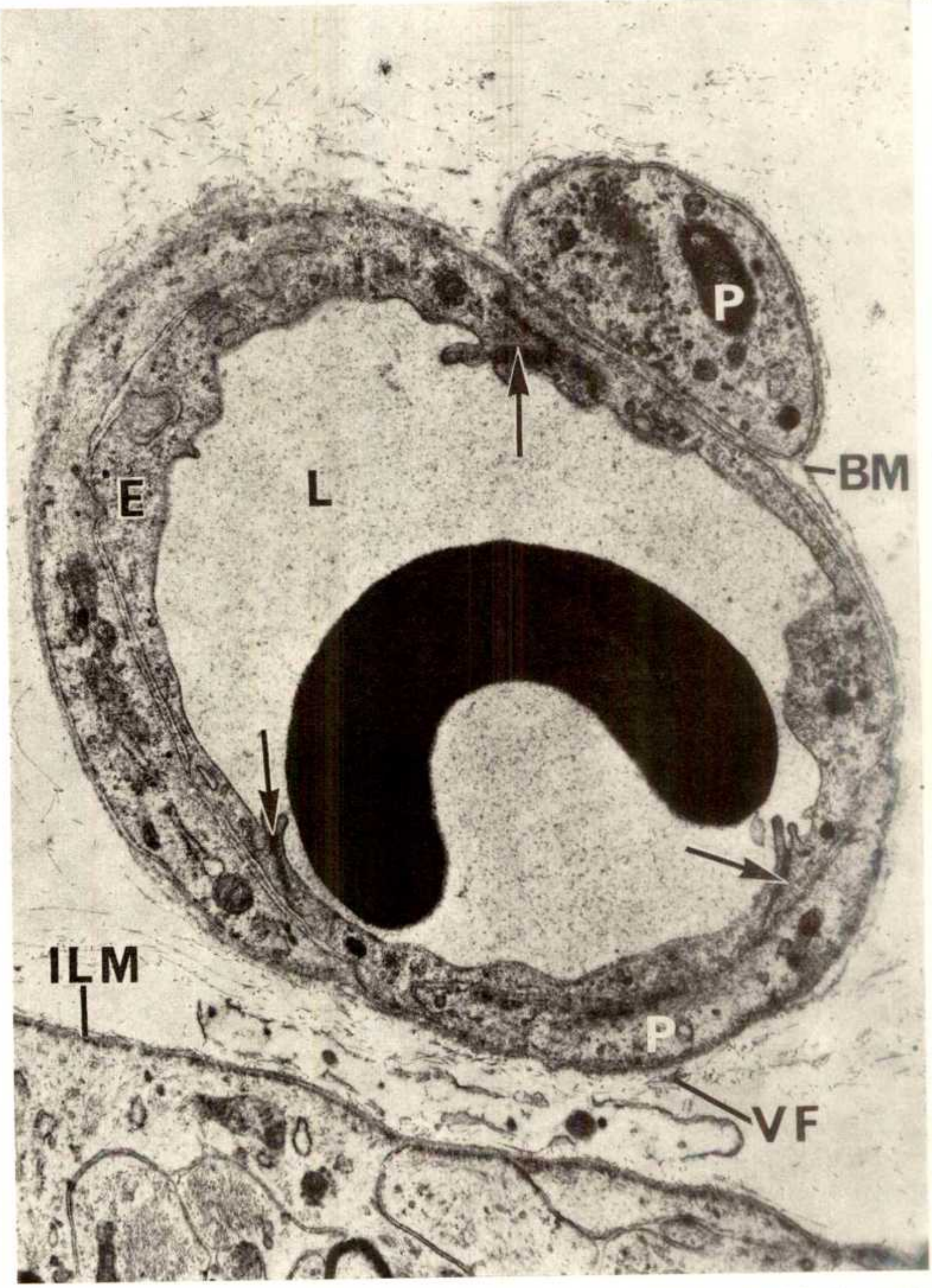

FIG. 5 *Electron micrograph of a blood vessel lying free in vitreous but close to the internal limiting membrane (ILM).* × 16,000

L = lumen E = endothelium with cell junctions arrowed
P = intramural pericyte
BM = basement membrane of the blood vessel
VF = vitreous fibrils

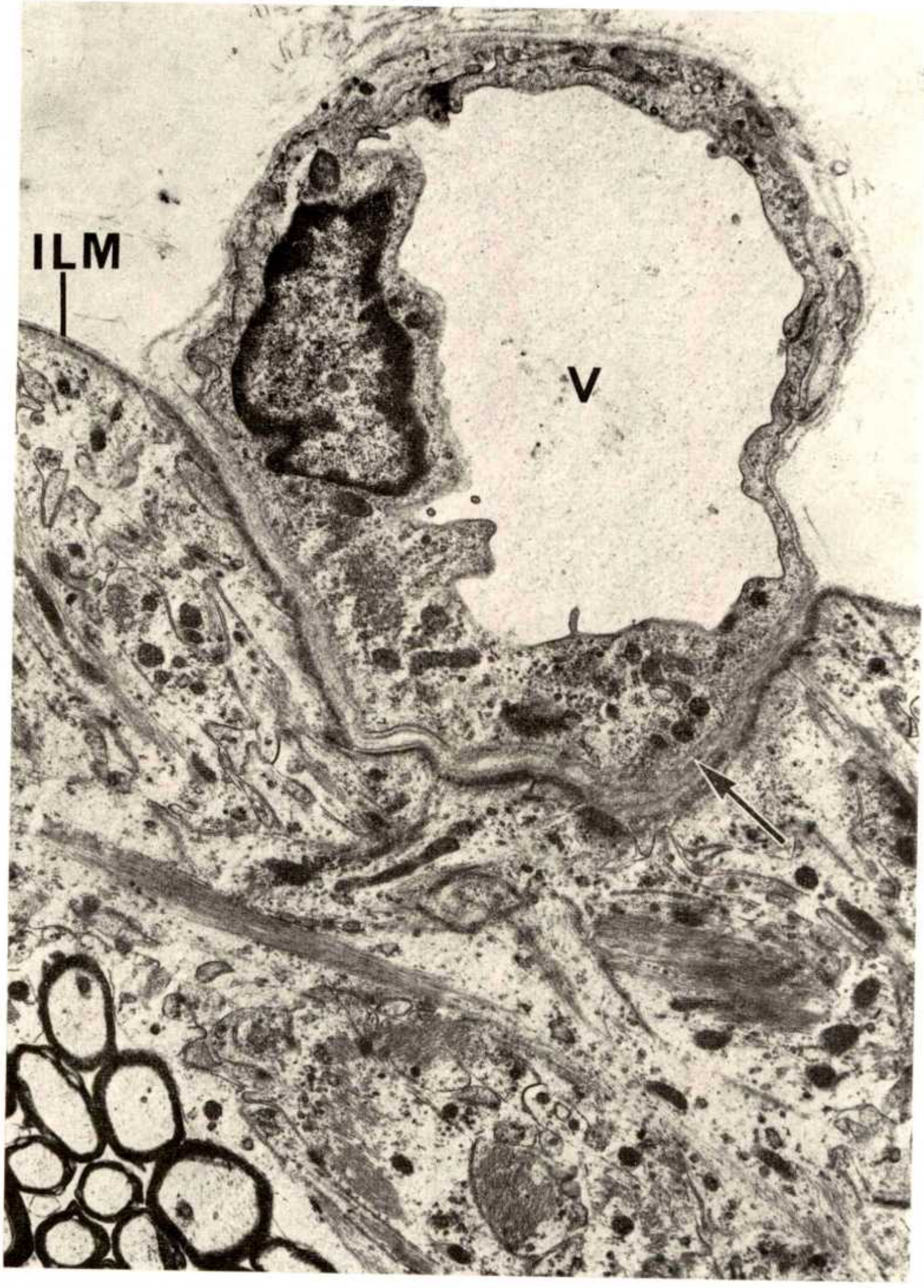

FIG. 6 *Electron micrograph of a blood vessel (V) dipping into the surface of the retina and indenting the internal limiting membrane (ILM). Note that the basement membrane in places appears to fuse with the internal limiting membrane (arrow) while in other places the two can be recognised distinctly.* × 11,000

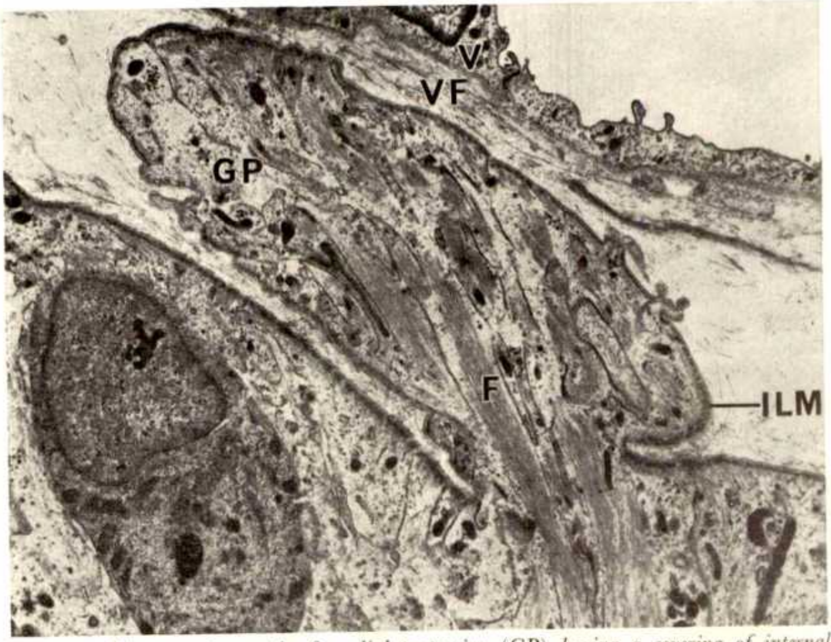

FIG. 7 *Electron micrograph of a glial protrusion (GP) having a covering of internal limiting membrane (ILM) and coming in contact with the blood vessel (V). Note the longitudinal arrangement of the intracellular fibrils (F) extending through the narrow neck of the glial protrusion.* × 6,650

VF = vitreous fibrils interposed between the internal limiting membrane covering the glial tuft and the basement membrane of the blood vessel

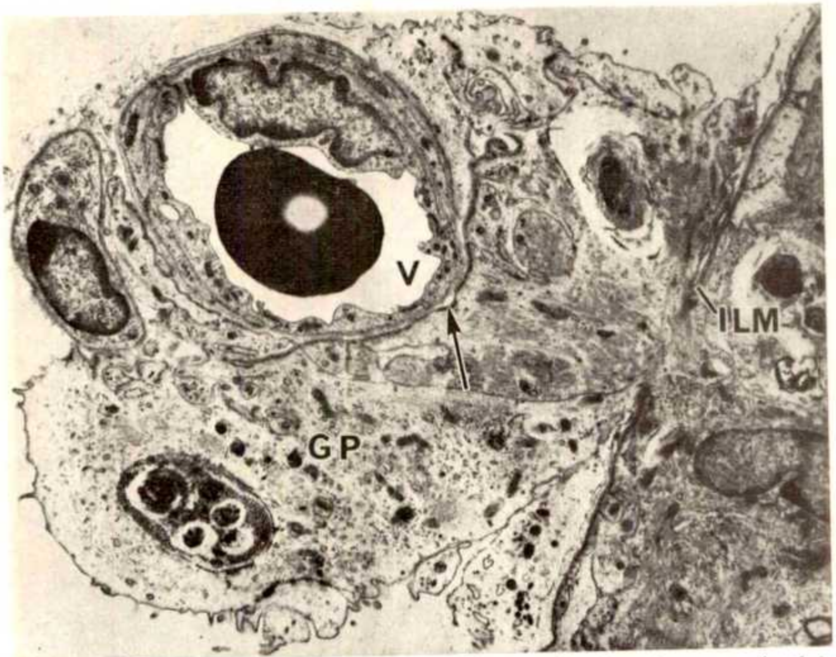

FIG. 8 *Electron micrograph of a glial tuft (GP) protruding through a narrow break in the internal limiting membrane (ILM) and enwrapping a blood vessel (V). Note the remains of the internal limiting membrane (arrow) in contact with the basement membrane of the blood vessel.* × 4,800

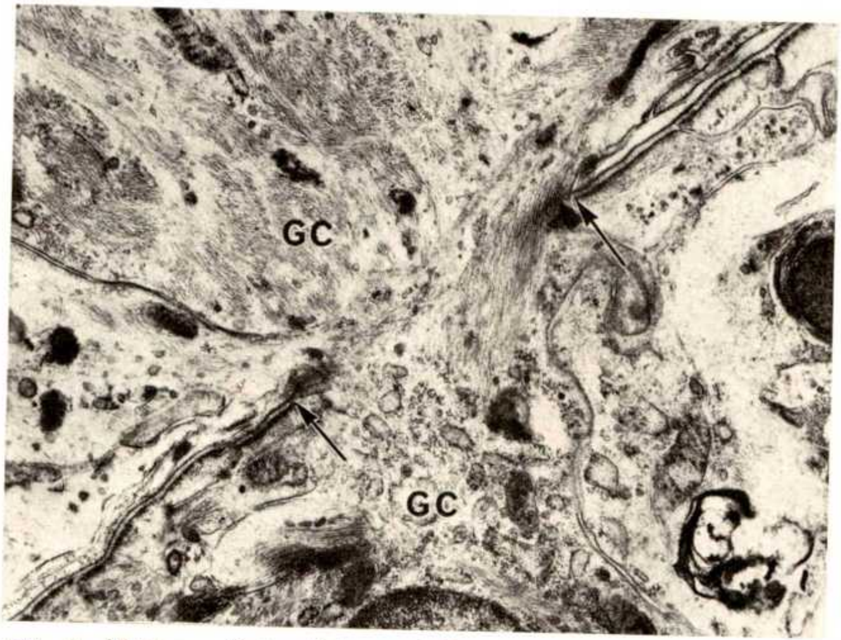

FIG. 9 *Higher magnification of the area in Fig. 8, showing the break in the internal limiting membrane (arrows) and the cellular continuity of the glial cells (GC) through the opening.* × 16,650

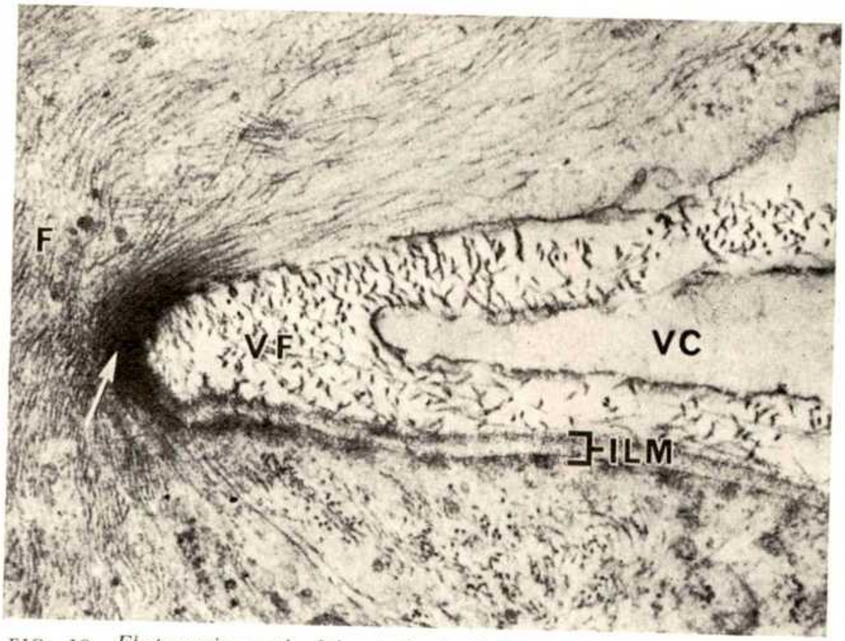

FIG. 10 *Electron micrograph of the opening in the internal limiting membrane (ILM), showing the arching and condensation (arrow) of the intracellular fibrils (F) of the glial cell.* × 50,000

VF = vitreous fibrils VC = pseudopod of a vitreal cell

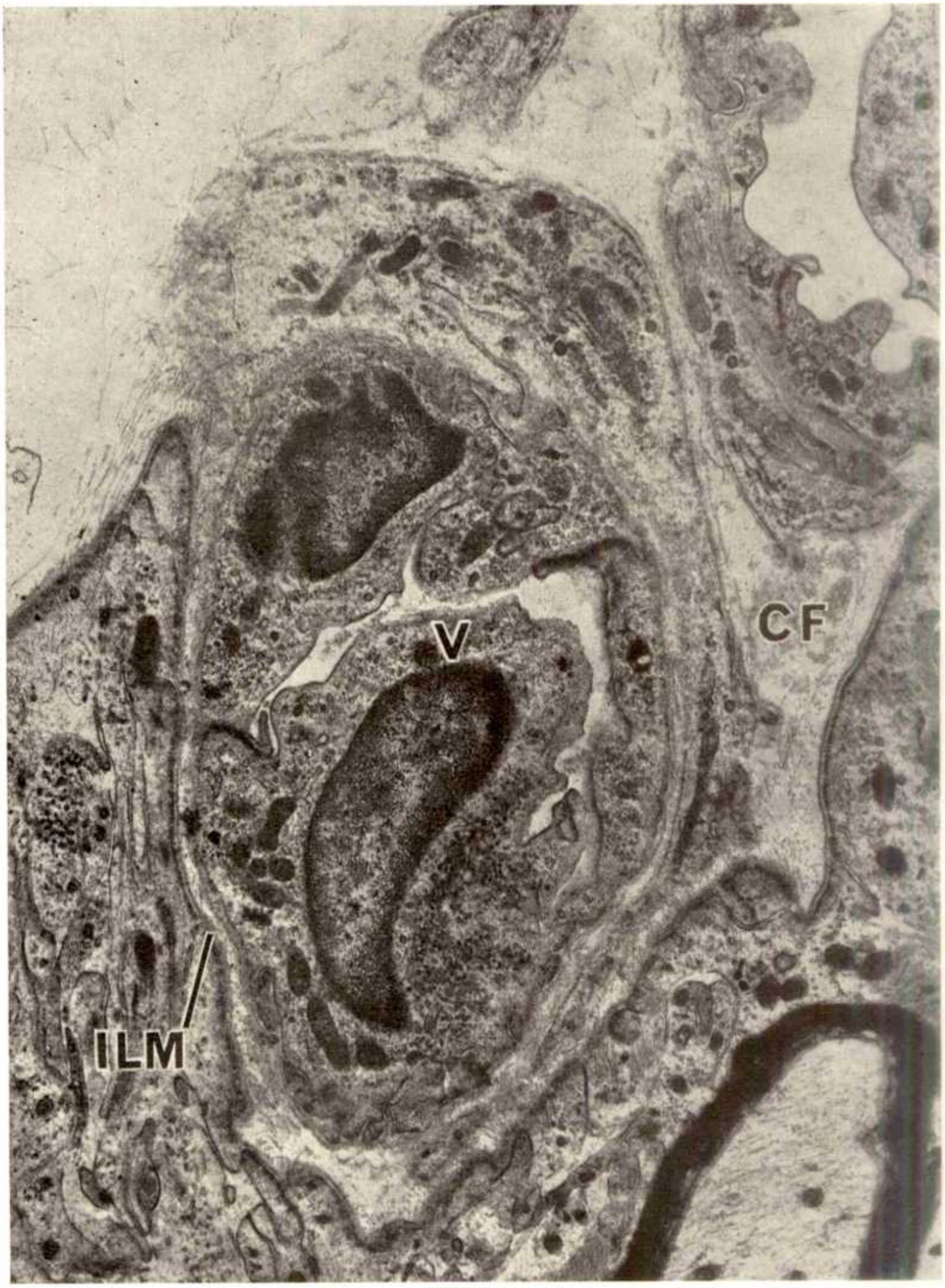

FIG. 11 *Electron micrograph, showing a blood vessel (V) encupped within an invagination of the internal limiting membrane (ILM).* × 15,000

CF = collagenous fibrils interposed between the internal limiting membrane and the basement membrane of the blood vessel

It is clear that, while the superficial vessels in the main lie vitreal to the internal limiting membrane, free within the vitreous, their basement membranes occasionally lie directly upon the basement membrane of the internal limiting membrane, and at frequent intervals the vessels are anchored to the retinal surface by glial attachments, which protrude from the retina, often enclasping and sometimes almost completely surrounding the vessels. With this knowledge of the fine structure it was interesting to re-examine conventional paraffin sections stained with haematoxylin and eosin and to find that these glial attachments may readily be recognized (Fig. 12).

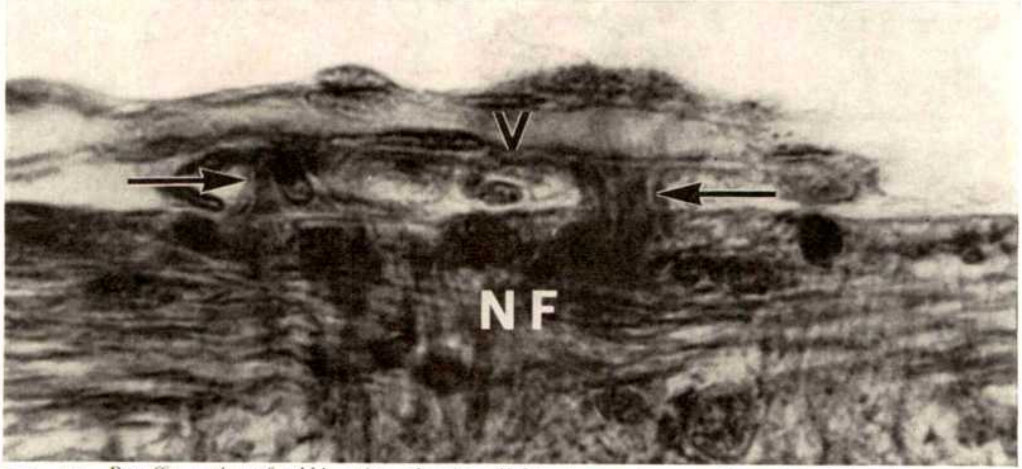

FIG. 12 *Paraffin section of rabbit retina, showing glial protrusions (arrows) in contact with and surrounding a blood vessel (V) cut longitudinally. Haematoxylin and eosin.* × 800
NF = nerve fibre layer

As we have shown, superficial vessels may occasionally appear to enter the retina, but actually they lie within invaginations of the internal limiting membrane from which they are separated by collagenous fibrils. In a subsequent paper providing a more detailed account of the rabbit's retinal vessels, we shall show that this is true also of the deep capillary branches which loop down into the nerve fibre layer so that in fact none of the vessels of the rabbit retina lies strictly within the nervous tissue. This vaso-glial structure corresponds with that described in the optic nerve of the monkey (Anderson, 1969, Fig. 4), which accords with the point made by Rohen (1954) that, since the medullated fibres of the rabbit are actually a forward extension of the optic nerve, the vessels are to be regarded as a vascular system of the nerve rather than of the retina.

At what developmental stage the glial tufts first appear has not yet been determined: they may exist before the vessels develop, or grow to embrace them as they proliferate along the retinal surface, or result from traction by the vessels at points where they were adherent to or were embedded in the retinal surface. Finally, it is interesting to note that similar glial tufts have been observed by conventional microscopy in cases of persistent hyperplastic vitreous (Hagedoorn and Sieger, 1956; Manschot, 1958) and by electron microscopy in experimental retrolental fibroplasia (Ashton, 1968), but whether there is any relationship in their genesis is at present unknown.

We acknowledge with thanks a grant from the Medical Research Council which has enabled the above work to be carried out. We are also grateful to Miss Angela Stone for technical assistance and Miss E. FitzGerald for secretarial help.

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Ophthalmoscopic appearances after injury to the circle of Zinn

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Concussion injury to the globe, if not severe enough to rupture the outer coat, causes a temporary expansion of the posterior sclera. This may pass unnoticed without producing any lesion, or may be severe enough to rupture the adjacent vascular structures. The circle of Zinn, by its particular situation around the optic nerve and within the sclera, is liable to such injury and its rupture is a possible cause of clinical appearances seen in some of the following eight cases. In the other cases there is probably a similar lesion of a short posterior ciliary artery or cilio-retinal vessel.

Case reports

(1) **A young man aged 22 years** received a direct blow on the left eye from a book, and at once noticed blurring of the central vision. The case was diagnosed as one of central retinal detachment with a possible macular tear. When I saw him 3 days after the accident there appeared to be a choroidal haemorrhage around the disc involving the macula.

Ophthalmoscopically a dark area intermingled with a dull-greyish elevation encircled the disc which was of a normal colour, and extended on the temporal side to reach the central area. The retinal vessels were running normally over the elevation and there was no sign of involvement of the overlying retina. The central vision was 1/60.

Conservative treatment in the form of rest and vitamin C was advised, but after one month there was no improvement of vision, which remained 1/60 with a marked scotomatous temporal field defect. The ophthalmoscope now showed that the dark and greyish elevation had absorbed, leaving an irregular peripapillary fibrosis with an intact overlying retina and retinal vessels (Fig. 1, col. pl.). The optic disc showed typical atrophic changes.

FIG. 1 *Irregular peripapillary fibrosis. Optic disc atrophic* (*Case* 1).

FIG. 2 *Peripapillary pigmentation with choroidal atrophy after removal of intraorbital tumour* (*Case* 2).

FIG. 3 *Well defined choroidal scar bespattered with pigment below atrophic disc* (*Case* 3).

FIG. 4 *Triangular pigmented patch with its base at the temporal disc margin, with an attempt to encircle the disc on the nasal side* (*Case* 4).

FIG. 6 *Area of irregular choroidal pigmentation on temporal side of left disc* (*Case* 6).

FIG. 9 *Linear area of choroido-retinal atrophy extending from the disc margin to the macula in the classical position of a cilio-retinal vessel* (*Case* 8).

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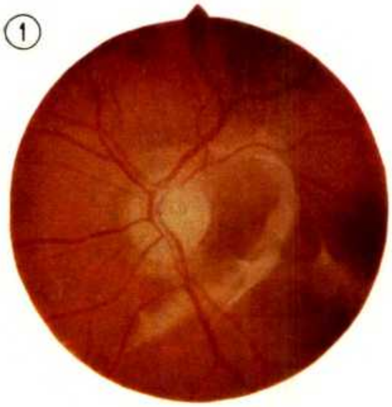

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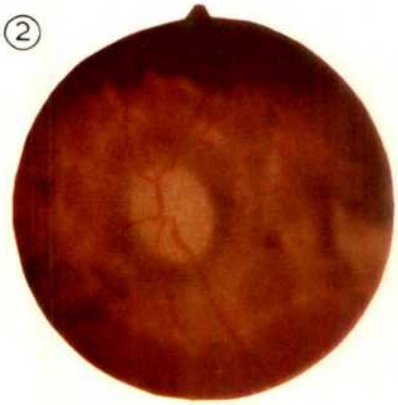

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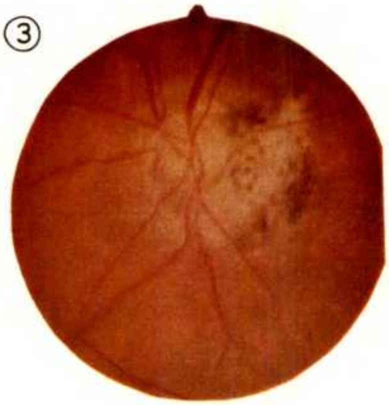

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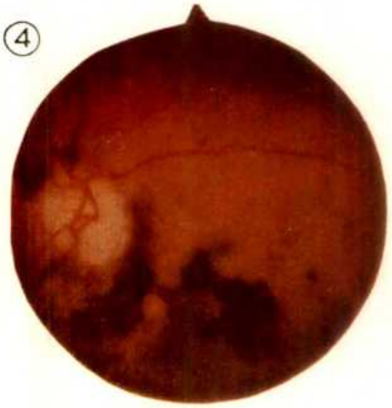

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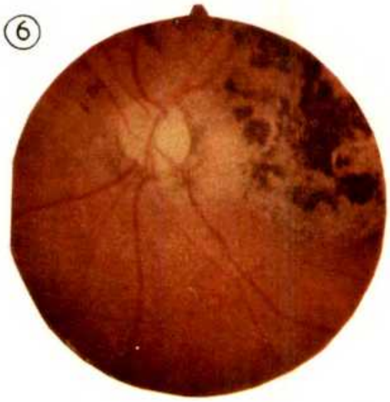

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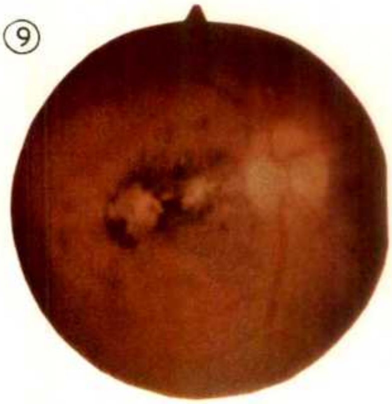

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(2) **A young girl aged 18 years** had had a successful removal of a seemingly benign orbital mass. One month later, when the eye was uncovered, she noticed marked diminution of vision, which was 1/60 with scotomatous defects in the nasal and temporal fields.

Ophthalmoscopic examination revealed a peripapillary greenish-grey pigmentation (Fig. 2, col. pl.). The retinal vessels passed normally over the lesion but the macular area was encroached upon. The disc showed a slight degree of atrophy. The diagnosis was peripapillary choroidal atrophy and fibrosis after a haemorrhage resulting from compression of the globe during the removal of the orbital mass.

(3) **A man aged 35 years,** during a routine refraction, was found to have had defective vision in the left eye for several years. He gave a history of a blunt injury to this eye 10 years before, after which he had had a rapid diminution of vision. No treatment was effective at the time.

Ophthalmoscopically a well-defined scar area bespattered with pigment was detected below an atrophic disc. There was a narrow extension of the scar around the disc on its upper margin (Fig. 3, col. pl.). The retinal vessels passed uninterruptedly over the affected area.

(4) **A woman aged 23 years** complained of marked diminution of central vision which was found to be counting fingers at 1 m. The nasal field was markedly affected and there was a tendency to diverge on occlusion of the eye. The left eye was normal. She stated that she had suffered a direct blow on the right eye by a blunt object 5 years before. Immediately after the accident she had noticed blurring of vision. No treatment was effective, and the vision gradually deteriorated.

Ophthalmoscopic examination revealed a triangular patch with masses of pigment, the base being at the lower temporal quadrant of a pale disc and the apex towards the periphery. There was a smaller pigmented area at the opposite edge of the disc and the macular region was besprinkled with pigment (Fig. 4, col. pl.). The retinal vessels passed uninterruptedly over the lesion.

(5) **A young man aged 18 years** received a direct hit on the left eye while playing football. As the blurring of vision which followed the injury was slight he did not trouble to consult a specialist, but he noticed that the visual acuity of the two eyes was gradually becoming unequal. The acuity of the right eye was 6/6 and that of the left 6/18 one year after the accident.

Ophthalmoscopic examination revealed a well-defined irregularly-pigmented atrophic patch close to the upper temporal margin of the disc. The retinal vessels passed uninterruptedly over the patch. The colour of the disc was normal (Fig. 5).

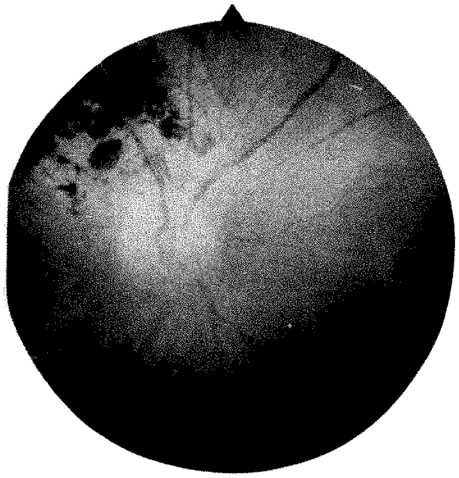

FIG. 5 *Well-defined irregularly-pigmented atrophic patch close to upper temporal margin of disc (Case 5).*

(6) **A boy aged 12 years** was found to have weak vision in the left eye (6/60 with correction) at a routine refraction. He was a high hypermetrope, about + 6 D sph. in both eyes. His parents said he had suffered a direct hit on the left eye by a tennis ball one year before. He had had only slight blurring of vision and treatment had been concentrated on the chemotic lids and conjunctiva.

Ophthalmoscopic examination revealed a well-defined round area of irregular pigmentation on the temporal side of the disc, extending to the macular region. Similar pigmented clusters were observed on the upper edge of the disc and there was a halo of choroidal atrophy surrounding the atrophic optic nerve head. The retinal vessels passed normally over the affected region (Fig. 6, col. pl.).

(7) **A young man aged 25 years** was refused a job because of weak vision in the right eye, 1/60 with eccentric fixation and field defects especially temporally and downwards. He said he had suffered a blow on this eye by a blunt object 5 years before.

Ophthalmoscopic examination showed a well-defined ring of peripapillary choroidal atrophy bespattered with a dark-greenish pigmentation. The ring was irregularly placed around the disc, extending more on the temporal side, less on the inferior margin, and much less on the upper nasal border. There was a tongue-shaped extension towards the macula which showed a marked stippling (Figs 7 and 8). The retinal vessels passed normally over the affected area. The remaining fundus showed no such patches.

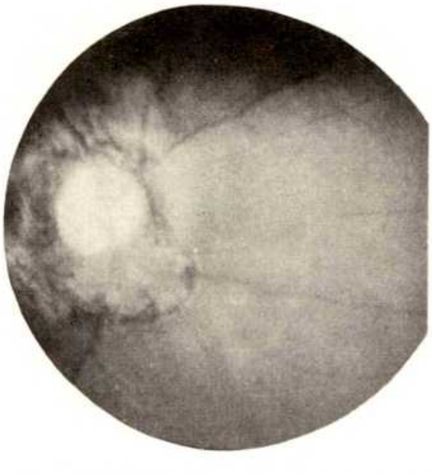

FIG. 7 *Ring of peripapillary choroidal atrophy besprinkled with dark-greenish pigmentation (Case 7).*

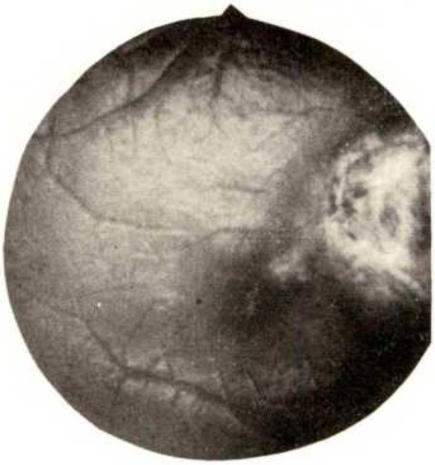

FIG. 8 *Extension of choroidal ring of Fig. 7 towards the macula (Case 7).*

(8) **A woman aged 30 years** complained that the left eye tended to diverge. The visual acuity in this eye was counting fingers at 1 m. with eccentric fixation. She said that 10 years before she had received a blow from her child's fist, and that this had been followed by blurring and gradual diminution of vision, which did not respond to treatment. Central choroiditis was the provisional diagnosis but no cause was found.

Ophthalmoscopic examination revealed a linear area of choroido-retinal atrophy extending from the temporal margin of the disc to the macula. The area was fringed with irregular pigmentation which divided the patch into nearly equal parts. A retinal artery passed uninterruptedly over the upper border of the lesion. The linear chorio-retinal scar was situated in the classical position of a cilio-retinal artery. No similar patch was present in the rest of the fundus. The disc showed some degree of atrophy (Fig. 9, col. pl.).

Discussion

The short posterior ciliary arteries as they pierce the sclera give branches which anastomose to form an arterial circle within the sclera around the optic nerve head. This circle of Zinn-Haller may also receive contributions from the most distal portion of the pial arterial plexus. Rarely, the circle of Zinn may be replaced by another circle placed slightly posteriorly within the dura. The circle of Zinn gives out branches to the pial sheath of the optic nerve, to the region of the lamina cribrosa thus contributing to the vascularization of the optic nerve head, and branches which pass into the peripapillary part of the choroid where they become associated with the small branches of the short posterior ciliary arteries which turn back into this region from the main part of the choroid. The cilio-retinal artery, which appears ophthalmoscopically at the margin of the disc and usually on its temporal side, is an inconstant branch of the circle of Zinn. It is concerned with the supply of a portion of the retina between the disc and the macula. Although the anatomical evidence in the literature of the existence of the cilio-retinal artery is scanty, Wybar (1954) demonstrated it in a neoprene cast. Together with the circle of Zinn, the posterior choroid is supplied by certain ciliary arteries which, instead of passing forwards, terminate near the site of perforation by the dichotomous formation of arterioles which finally break up to form the choriocapillaries. As for the segmental localization within the choroid, it has been suggested that distinct specialized zones are present. These constitute the equator, the periphery, the submacular, and the peripapillary zone (Wybar, 1954). This probably applies to the arteries which run in sectors without anastomosing with their neighbours, but the continuity of the choriocapillaries over the entire choroid is complete. A continuous network in the peripapillary zone, composed of arterioles which do not participate in the vascular supply of the rest of the choroid, was described by Marin-Amat (Discussion of Bartolozzi, 1952).

The first mention of a lesion of a short posterior ciliary artery was made by Coats (1907), who referred to a case reported by Knapp (1868) of a woman suffering from mitral regurgitation and cardiac hypertrophy who experienced failure of vision in both eyes after two attacks of giddiness. In the first attack there was a diffuse greyish opacity in the right retina around the macula and below the nerve; in the second attack a retinal opacity was found above the left macula. Both retinal lesions cleared up in 3 to 5 days. Knapp's explanation of the phenomena was that on both occasions the endocarditis had given rise to emboli which had lodged in some vessel of the brain and also in the posterior ciliary arteries. It is more likely that the condition was a spasm of branches of the central retinal artery; the part played by the short posterior ciliary arteries is rather controversial. Coats (1907) also described the histopathological appearance of an eye removed as a result of iridocyclitis with secondary glaucoma; because of the presence of extensive necrosis and inflammatory infiltration of the sclera, choroid, and retina, he concluded that the patient's symptoms were best explained as an obstruction of a posterior ciliary artery with a consequent infarction of the inner layers of the sclera, choroid, and retina. There was no history of trauma in either case.

Bartolozzi (1952) presented a case of post-traumatic peripapillary choroidal atrophy which he attributed to rupture of the finest arterial branches of the posterior ciliary arteries. In the ensuing discussion Marin-Amat (1952) agreed with the diagnosis and suggested that the peripapillary choroidal atrophy was pathognomonic of deficient circulation in that region. According to him the arborization of the short posterior ciliary arteries nearest to the papilla resolves into a continuous arterial network which supplies blood to the peripapillary zone of approximately the diameter of the papilla. He concluded that the forward stretching of the eyeball as a result of posterior trauma explained the rupture of the fine branches of the short posterior ciliary arteries. A torsion of the eye resulting from such trauma was suggested by Bartolozzi (1952).

By the "continuous arterial network", Marin-Amat probably meant the circle of Zinn.

In discussing the sequelae of contusion of the posterior pole on the papilla, Bonamour, Brégeat, Bonnet, and Juge (1968) stated that ophthalmoscopically their intensity paralleled that of the primary papillary and peripapillary manifestations. The papilla usually retains a normal aspect, but when the trauma is severe a cicatricial peripapillary degeneration appears in the subsequent months. In its early form, this degeneration is seen as a ring of pigment with bluish reflexes around the disc associated with a semi-annular paracentral scotoma. At a later stage pigment migration is associated with a band of a peripapillary atrophy. The pigment is gathered at the centre of this band or disposed on its edges. No explanation is given to this clinical picture or how it is developed.

Duke-Elder (1954) mentioned a clinical picture wherein a spherical, yellowish area with well-defined margins, which subsequently showed proliferation of the retinal pigment associated with a scotoma, developed after contusion injuries. This appearance was said to be due to ischaemia brought on by rupture of the posterior ciliary arteries; somewhat similar appearances were produced experimentally in animals by section of the posterior ciliary arteries.

The cases reported above demonstrate a peculiar ophthalmoscopic appearance after a contusion injury to the eye. Cases 1 to 7 showed a limited choroidal lesion either around the disc (Cases 1, 2, 3, 6, and 7) or extending from the disc region (Cases 4 and 5). An extension of the lesion to involve the macular area is seen in Cases 1, 6, and 7. The choroidal lesion is usually an atrophic patch irregularly bespattered with pigment, and varying in colour from black to grey or greenish-grey. In all cases, the retinal vessels passed uninterruptedly over the choroidal atrophic patch.

Most of the patients were seen a long time (from 1 to 10 years) after the injury, and therefore show the final and permanent fundus picture. Only in Case 1 were both the very early stage of the choroidal lesion and the late result observed. In all cases there was no other similar lesion in the same or in the contralateral one, and in every case there was a definite history of trauma followed by blurring of vision. No further investigations have been carried out because the defective vision and ophthalmoscopic appearances were related to the trauma. Treatment was ineffective and a permanent visual defect was the ultimate result.

Only in Case 8 was the condition mistaken for a central chorio-retinitis because the retina was involved, but the true cause was undetermined. This case is the only example of a retinal lesion due to injury to a vascular choroidal structure. The shape and the site of the lesion point to the involvement of an isolated cilio-retinal artery.

Because all these cases are directly related to a concussion injury and most of them show a peripapillary pigmented atrophic choroidal lesion and some a similar triangular or rectangular area in close contact with the disc margin, it appears that the lesion is due to a vascular derangement either of the circle of Zinn or of a short posterior ciliary artery. In Case 8 there was possibly an isolated cilio-retinal artery injury.

Treacher Collins (1917) believed that concussion injuries produced subchoroidal haemorrhage. The rupture of a short posterior artery is a plausible hypothesis for the production of such a haemorrhage.

Ashton (1952) suggested that capillary damage might be brought about primarily by an increase in the normal tissue pressure within a localized region of the choroid. A likely cause for such an increase in pressure is a haemorrhagic or inflammatory extravasation within the choroid; this exerts a marked effect on the choroidal vascular bed owing to the limitations imposed by the normal force of the intraocular pressure acting against the unyielding sclera.

The sequence of events following a concussion injury to the eye may be visualized as follows. The injury causes the posterior portion of the sclera to expand. This expansion may cause the rupture or occlusion of the vessels which perforate it perpendicularly or obliquely. A vascular channel like the circle of Zinn which is embedded in the sclera is more susceptible to such a lesion. Haemorrhage due to the rupture may cause secondary occlusion of the affected or neighbouring vessels. The haemorrhage or infarction which follows the secondary occlusion causes the characteristic darkening of the area supplied by the affected vessel, as in Case 1. When the condition subsides, atrophic degenerative changes set in, giving the characteristic appearance seen in all the cases. There is a regular well-defined area of choroidal atrophy with pigment bespattered irregularly either over the whole region or at its periphery. The fact that the retinal vessels pass over the affected region without interruption means that the retina is not involved in the primary lesion, but the scotomata which develop in most cases indicate that at least the posterior neuro-epithelial layers of the retina are secondarily affected.

Because the macula is involved in most cases, it is apparent that this region is supplied by a branch arising either from the circle of Zinn or from a short ciliary artery.

A similar peripapillary choroidal atrophy with pigmentary disturbance is often present in high myopia (Fig. 10), and this suggests the occurrence of some similar vascular derangement, probably a disturbance of the blood supply through the stretching of the posterior sclera, a constant process in the progressive type of this condition. There may thus be a vascular basis for the atrophic changes present in high myopia.

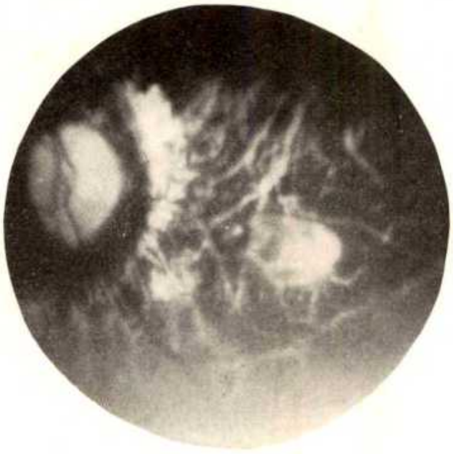

FIG. 10 *Peripapillary choroidal atrophy with pigment deposition in a case of high myopia.*

Summary

Eight cases are reported of peripapillary choroidal atrophy following trauma. Two other cases with the same ophthalmoscopic appearances were found in the literature. Injury to the circle of Zinn or to a short posterior ciliary artery may be due to expansion of the posterior sclera after concussion trauma to the eye. The relationship of this hypothesis to the segmental arrangement of the blood supply to the choroid is discussed.

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Retinoblastoma

A study of 139 cases

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The successful treatment of retinoblastoma with *x*-rays was first reported by Hilgartner (1903). Subsequently Foster Moore (1929) in London and Martin and Reese (1936) in New York confirmed that ionizing radiation could destroy this type of tumour, but the very high doses of radiation used by these earlier workers frequently caused severe complications sometimes leading to the loss of the eye.

From a study of the histological sections of eyes treated with radon seeds by Moore, Stallard, and Milner (1931), Stallard (1936) determined that a dose of 3,500r was lethal to retinoblastoma cells. Subsequent collaboration with Innes (1964) led to the development of Cobalt-60 applicators of varying size which could deliver a dose of 4,000r to the summit of the tumour in 7 days.

Because of the serious ocular complications and the occasional case of radiation-induced malignant change in neighbouring structures, Reese, Merriam, and Martin, (1949) gradually reduced their dosage of conventional *x*-rays from the original level of around 10,000r; they also independently confirmed that a dose of 3,500r (combined with chemotherapy) was lethal to most retinoblastomas (Reese, Hyman, Tapley, and Forest, 1958). This reduced dosage of radiation has enabled many of these patients to survive with cure of the tumour and with good vision in the treated eye (Ellsworth, 1968; Stallard, 1962, 1968; Cassady, Sagerman, Tretter, and Ellsworth, 1969).

Methods for the delivery of radiation have been improved since the earliest radon seeds and low-voltage *x*-rays; the former have largely been replaced by Cobalt-60 applicators whilst high energy Cobalt beam units and linear accelerators permit irradiation of the eye with little involvement of adjacent structures (Skeggs and Williams, 1966). In addition, light coagulation (Höpping and Meyer-Schwickerath, 1964) has proved useful for the treatment of small tumours, and more recently cryotherapy (Lincoff, McLean, and Long, 1967; Rubin, 1968) has been used successfully in similar cases.

The work of Gillette and Bodenstein (1946) demonstrated that developing retinal cells were especially susceptible to derivatives of the nitrogen mustard group of chemotherapeutic agents, one of which, triethylenemelamine (TEM), has been used extensively, particularly in New York, in conjunction with radiation, for the treatment of cases of advanced retinoblastoma (Ellsworth, 1968; Hyman, Ellsworth, Feind, and Tretter, 1968).

In this paper we have reviewed all the patients with retinoblastoma seen at this Unit since 1960. A total of 169 cases was seen and treated, thirty of which were not subsequently followed by us; as most of the latter had been referred from foreign countries for treatment and had subsequently returned home, they have been excluded from the analysis of results.

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The subject matter of this paper will be presented in three parts with a separate discussion for each.

I. PRELIMINARY ASSESSMENT

There were 73 males and 66 females, which confirms the observations of other workers that the sex incidence of retinoblastoma is essentially equal, as it should be if the disease is transmitted by an autosomal gene.

Almost 80 per cent. (111) of our patients had bilateral disease and 28 were unilateral, which would not be the case in a random sample. The high percentage of bilateral cases in this series reflects our interest in this disease and the frequent referral of patients to us after the second eye had become affected. The family history was positive in 38, negative in 76, and not recorded in 25 cases.

Table I is interesting because it shows that we see a considerable number of bilateral retinoblastomas in cases with no family history of the disease. Genetic studies (François and van Leuven, 1964) indicate that a sporadic case can arise as a result of:

(1) A germinal mutation affecting every cell and which can be bilateral;

(2) A somatic mutation occurring in the precursor retinal cells developing in one eye;

(3) A phenocopy which results in the tumour cells developing in one retina.

Table I *Comparison of family history and bilaterality in 114 cases*

Family history	*Unilateral*	*Bilateral*
Positive	22	54
Negative	2	36

The last two processes are usually held responsible for most sporadic cases and are always unilateral. It is, therefore, necessary to account for the high incidence in this series of bilateral cases with no family history. We do not usually investigate the family history of every patient in detail as this would be impossible without the assistance of a genetic team: therefore some of our patients, whose parents are unaware of any other member of the family with this tumour, may actually have a positive family history in a distant relative. Secondly, in about 20 per cent. of cases the gene will not penetrate completely, so that the mutation, having occurred in the parents, may not become manifest in the offspring. Thirdly, the referral of many patients when the second eye has become affected or who have bilateral tumours when first seen naturally overloads our statistics in favour of bilateral cases. However, the possibility remains that, in sporadic cases, unilateral or bilateral, there may be a germinal mutation or a positive family history which is not immediately apparent. It is of interest that we have two patients with a positive family history and unilateral disease, one with 18 months' and the other 5 years' follow up, who must nevertheless have a retinoblastoma gene in every cell in both retinae. We also have two other patients with no previous family history and whose siblings have developed retinoblastoma. Thus it is clear that every unilateral case must be followed lest a tumour develop in the other eye, and that all siblings and offspring of retinoblastoma patients must be seen soon after birth and subsequently at regular intervals.

Table II shows that the most frequent presenting abnormality recorded is a white appearance of the pupil, the next most common sign being the development of a squint. Rarely these patients are first seen because of a painful red eye due to secondary glaucoma with a shallow anterior chamber, raised tension, and rubeosis iridis.

We agree with Reese (1963) that retinoblastoma does not develop in a congenitally microphthalmic eye, but it is important to recognize that a phthisical eye may contain an active retinoblastoma. Two patients were seen with a spontaneous hyphaema due to iris seeding not unlike that which occurs characteristically with juvenile xanthogranuloma, but at this stage a retinoblastoma almost fills the globe and the main bulk of it can be easily seen when the pupil is dilated. Most retinoblastomas have large feeder vessels which may, when associated with a solitary retinal tumour, lead to the erroneous diagnosis of a vascular tumour or malformation (Bedford and MacFaul, 1969); furthermore, the presence of exudates with such vascular changes does not exclude the diagnosis of retinoblastoma, especially in the younger age group.

Table II *Presenting symptoms*

Presenting symptoms	*No. of cases*
White pupil reflex	44
Squint	28
Painful red eye	6
Hyphaema	2
Several of the above	10
None (examined because of positive family history)	13
Not recorded	36
Total	139

Table III *Age at presentation*

All cases	Average	1 yr
	Range	1 mth to 5 yrs
Family history	Negative	1 yr 5 mths
	Positive	8 mths

The average age at first examination (Table III) is slightly younger than in the series reported by Howard and Ellsworth (1965), who emphasized that the majority are diagnosed in the first 2 to 3 years of life. In general, it is earlier when there is a positive family history and in our Unit these patients at risk are now examined before symptoms arise. In this way thirteen new asymptomatic cases have been found. Occasionally, however, these tumours arise in older children; thus, of 57 cases reported by Damaske and Jünemann (1969), five were over 4 years of age, and we have recently seen the first single primary tumour in a child aged 7 with a positive family history.

The most important factor, however, in the preliminary assessment is a comprehensive examination of the fundus. We follow the policy established by Reese and Ellsworth (1963). The children are examined under general anaesthesia with the pupils fully dilated. The fundi are examined to the ora serrata, using the binocular indirect ophthalmoscope with scleral depression, as many retinoblastomas arise anterior to the equator. A diagram is made showing the site and size of all tumours and any lesion that can be photographed is recorded in this way, as we have found photographs especially helpful in following suspicious areas after treatment. For follow-up purposes all cases are grouped according to the scheme proposed by Reese and Ellsworth (1963) (Table IV, overleaf), to which we have added Group 6 to include those cases with residual orbital disease after enucleation associated with optic nerve involvement or extrascleral extension.

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Table IV *Prognosis of retinoblastoma*

Group	*Prognosis*	*Characteristics*
I	Very favourable	Solitary and multiple tumours less than 4 disc diameters at or behind equator
II	Favourable	Solitary and multiple tumours 4 to 10 disc diameters at or behind equator
III		Any lesion anterior to equator Solitary lesion greater than 10 disc diameters behind equator
IV	Unfavourable	Multiple tumours greater than 10 disc diameters Any lesion extending anteriorly beyond the limits of ophthalmoscopy
V	Very unfavourable	Massive tumour involving more than half the retina Vitreous seeding
VI		Residual orbital disease Optic nerve involvement and extrascleral extension

After treatment the patient is examined in a similar manner initially at 3 to 4 weeks and then at increasingly longer intervals depending on the response to treatment. At the age of about 6 or 7 years the patients are seen without anaesthesia as out-patients and if all is well they are seen thereafter every 9 to 12 months indefinitely.

We do not normally examine older siblings if they have no ocular symptoms unless this can easily be done as an out-patient procedure. We do, however, examine all newborn siblings and offspring of retinoblastoma patients not later than 4 weeks after birth and then periodically depending on the likelihood of a retinoblastoma arising based on our knowledge of the family history. In all cases, however, the patient is seen at least four times during the first year, three times in the second year, every 6 months until the age of 6, and thereafter at yearly intervals. We stop seeing non-affected patients after the age of 10 years, but, as has already been mentioned, we follow treated and cured patients indefinitely in order to maintain contact with them, especially so that if the question of marriage arises, we can remind them of the possible hereditary nature of this disease. In this way also we can ensure that the children are examined as soon as possible after birth. We like to see newborn children at about 4 weeks of age, by which time they can be safely anaesthetized, and also because we have seen one child at 6 weeks with such an extensive tumour that local treatment was impossible. A further advantage of early examination is that in these young children the tumours are usually small and easily treated, often without recourse to irradiation of the eye.

II. PRINCIPLES OF TREATMENT

In this section we outline the various modalities of treatment that are at present available and our reasons for using each type. The treatment of retinoblastoma in England was initially based on focal irradiation culminating in the development of the Cobalt plaque, but it has become apparent that this form of treatment has some limitations; consequently there are definite indications for irradiation of the whole retina. The cases reviewed in this report include some treated during the period when the indications for total retinal radiation were being established.

COBALT APPLICATORS

These have the advantage that a continuous dose of radiation can be delivered to the tumour with little spread to the surrounding ocular structures. A dose of 20,000r to the sclera and choroid and 4,000r to the summit of the tumour can be delivered in 7 days. A chorio-retinal scar with resulting nerve fibre damage develops at the site of treatment. Cobalt applicators, therefore, should not be placed under or adjacent to the macula. We have also found that this dose of radiation cannot be tolerated by the major retinal vessels in the vicinity of the optic disc as severe vitreous haemorrhages often result (MacFaul and Bedford, 1970). For this reason we no longer use the C-shaped plaque which was designed to embrace the optic nerve, and we rarely place a circular plaque closer than 5 mm. to the optic disc. In this series nine C-shaped plaques were used and six cases also had either another plaque or whole-eye irradiation; in eight of these severe vitreous haemorrhage resulted in the loss of the eye or blindness from haemorrhagic glaucoma; only one boy in this group has retained normal vision and attends a normal school. Some of these haemorrhages resulted from the ill-effects of combined radiotherapy, but we feel that the risk of haemorrhage is significantly increased by C-shaped plaques and that tumours near the disc and macula are therefore best treated by external radiation. At present the indications for the use of a Cobalt plaque include single tumours less than 13 mm. in diameter or two separate tumours or groups of tumours that need no more than one 10 mm. plaque each, provided that the lesions are away from the optic disc and macula.

EXTERNAL BEAM THERAPY

Our method of external radiation with the Cobalt beam using a direct anterior field, which was developed by Skeggs and Williams (1966), has the advantage of treating the whole retina and vitreous without involving the other eye in a significant dose of radiation; in this way each eye can be treated independently. This type of radiotherapy is indicated for large tumours (over 13 mm. in diameter), multiple tumours of any size scattered over the retina, tumours with vitreous seeding, and tumours of any size near the optic disc. A total dose of 4,000r will destroy most retinoblastoma cells with as yet little clinical evidence of damage to normal retina elsewhere. Frequently, tumours which initially covered the macula will regress, leaving a relatively normal fovea with a good visual acuity. As more of these children survive, it will be essential to carry out electrodiagnostic tests to determine whether there is any subclinical damage to retinal function. With this form of radiation, of course, the normal ocular structures and brain are irradiated and a cataract of varying density inevitably develops within about 18 months (MacFaul and Bedford, 1970). This complication is amenable to surgical treatment and its management will be discussed in a subsequent report. A temporal approach with the linear accelerator is useful if the other eye has already been removed; otherwise it also would receive a large dose of radiation. However, the use of this method in an attempt to spare the lens also spares the anterior retina and vitreous from the full therapeutic dose—a region where many tumours first appear. We do not recommend this technique except for localized tumours at the posterior pole in an only eye.

LIGHT COAGULATION

This can be used to treat tumours 1 to 4 mm. in diameter, provided that they are not close to the macula or temporal edge of the disc where the resulting damage to the nerve fibres would produce a large scotoma. We have found this method particularly useful with small recurrences following Cobalt plaque or beam therapy, thereby avoiding further radiation and its associated complications.

CRYOTHERAPY

This, when performed through the conjunctiva, has also proved valuable for the destruction of small tumours and recurrences, particularly those in the peripheral retina which may be difficult to reach adequately with the light coagulator.

CHEMOTHERAPY

This has been used extensively in some centres (Hyman and others, 1968); oral cyclophosphamide was used here up till 1966, but was then discontinued with no apparent adverse influence on the subsequent results. There is some doubt whether a significant concentration of cytotoxic drugs in the eye is reached after oral administration and we await with interest the results of treatment with these substances by the arterial route.

ENUCLEATION

We consider each eye separately and try to save both if there is any chance of restoring or preserving useful vision. In bilateral cases we do not necessarily remove the most severely affected eye and, as with unilateral cases, the only indication for enucleation is involvement of the optic nerve which is either clinically obvious or must be inferred from the presence of opaque media, shrinkage, or enlargement of the globe. It should, however, be emphasized that the total retinal detachment often seen with anteriorly-placed tumours is amenable to whole-eye radiation with an anterior field and does not demand immediate enucleation. At a later stage, however, enucleation may be required if the tumour has failed to respond to treatment or if the eye has been damaged by intraocular haemorrhage, secondary glaucoma, or other complications of irradiation (Table V). We do not insert an implant into the socket after enucleation because this prevents adequate palpation of the orbit at follow-up examination.

Table V *Enucleation*

No. of cases seen	139	
Primary enucleation	7	
Enucleation after conservative treatment		
Active tumour	9	22
Radiation complication	13	
Tumour active at death	2	
No. of cases in which eyes were saved	108	

III. RESULTS

Before 1967 patients were not classified according to the scheme by Reese and Ellsworth (1963) (Table IV). Since then, however, all patients have been classified at the first examination, although we do not entirely agree with the prognostic significance hitherto attached to each of these classes. Tumours anterior to the equator, which may frequently be seen only by indirect ophthalmoscopy and scleral depression, do not invariably carry a worse prognosis merely because of their peripheral position. Such small tumours (1–4 mm.) can easily be treated with cryotherapy, whilst moderately-sized tumours (4–8 mm.) can be dealt with by the application of a Cobalt plaque and even larger tumours anterior to the equator can ideally be treated with a Cobalt beam using the anterior field. With peripheral tumours, therefore, the prognosis depends more on the size of the lesion than on its exact site. It is probable that this difference of opinion stems from the different route of radiation used by the New York Group; we do not use a linear accelerator with a temporal field in an attempt to spare the lens because this approach must also spare the peripheral retina, where many tumours first arise, from the full therapeutic dose of radiation. Furthermore, we have found that the presence of vitreous seeding does not invariably carry a poor prognosis. In our view this situation also is unsuitable for the use of a temporal field for the reasons previously stated.

The success rate, using all forms of treatment in each class, is 100 per cent. in classes I and II, 86 per cent. in Class III, and 75 per cent. in Classes IV to VI. The follow-up in this series has been continued for 2 years or more in 66 per cent., and for over one year in 81 per cent. It is our impression that the majority of tumours which appear inert for 9 months or more are probably cured, but the exceptions emphasize the necessity for continuous supervision.

A total of 132 cases was treated; eleven of these were children who have subsequently died, leaving 121 patients who are at present alive and well (Table VI).

Table VI *Recurrence*

Therapy		*Cobalt beam*	*Focal*
No. of cases treated		58	63
No. of cases with recurrence		28 (46 per cent.)	27 (42·8 per cent.)
Time when recurrence treated (mths)	Average	10	6
	Range	At once to 22	24–4
Treated by enucleation		9	5
Eyes saved		19	22
Recurrence after second treatment		6	4

RECURRENT TUMOUR

Recurrence continues to be a problem because a second dose of radiation may result in severe intraocular haemorrhage and glaucoma (Table VI). In this series we have a big recurrence rate after whole-eye radiation (46 per cent.), but this does not mean that the focal method of treatment is more effective as the whole-eye method is essential for the more advanced cases and larger tumours are inevitably more difficult to destroy. It is generally true that if treated tumour appears inert for 6 to 9 months it can be regarded as cured, but exceptions occur and a recurrence has been noted as long as 2 years after treatment; this again emphasizes the importance of maintaining close supervision of all patients even when they appear to be doing well.

Our policy for the treatment of recurrent tumour is to avoid further radiation if the lesion is small enough to be destroyed by light coagulation or cryotherapy. A Cobalt plaque can be applied to an eye which has already received Cobalt beam therapy, but two courses of whole-eye radiation are undesirable in view of the severe damage which follows when a total dose of 6,000—7,000r is exceeded. Most of our children are too young at present to permit formal testing of the visual acuity, but in nineteen cases with treated and cured recurrent tumours followed for more than one year, ten have vision good enough to permit normal schooling, two have sufficient to get around and play, and the remaining seven have light perception only. It should be noted in the last group that poor vision has, in some cases, resulted from macular damage due to the disease. At present we can say that eyes receiving a second course of radiation will probably do worse visually than those in which a recurrence can be destroyed by light coagulation or cryotherapy; it will need a longer period of follow up and the evaluation of more cases before we are able to predict the chances of retaining good vision after repeated radiotherapy.

NEW PRIMARY TUMOURS

Retinoblastoma is a tumour of multi-focal origin in one or both eyes, and in view of this Reese (1963) advocated irradiation of the whole retina. Our series includes 63 cases treated initially by focal means—Cobalt plaque, light coagulation, or cryotherapy—in the area of the tumour alone. We have analysed these cases for the incidence of new primary tumours as opposed to recurrences at the site of the original lesion (Table VII).

Table VII *New primary tumours after treatment*

Treatment	*Focal*	*Whole-eye*
No. of cases treated	63	58
No. with new primary tumour	12 (20 per cent.)	5 (8 per cent.)
Average time of appearance (mths)	4	10

In fact, sixteen new primary tumours were found in the twelve cases of recurrence after focal treatment, and they were dealt with by light coagulation or cryotherapy (7), Cobalt plaque (8), and Cobalt beam (1).

Three of the new primary tumours appearing after whole-eye radiation responded to a small Cobalt plaque, but in the other two cases enucleation was felt to be the only safe course.

These figures confirm the multicentric origin of retinoblastoma in one or both eyes. It is our opinion, however, that the appearance of new tumours in only 20 per cent. of eyes treated originally by focal means is not high enough to justify irradiation of the entire retina with the object of destroying subclinical foci. In our experience many of these new primary tumours can be successfully destroyed by the application of a small (5 mm.) Cobalt plaque, by light coagulation, or by cryotherapy. With careful follow up these new tumours can usually be detected while they are still small and easily controlled by these focal methods.

Summary

(1) The history of the various forms of treatment for retinoblastoma is briefly noted.

(2) The presenting symptoms and signs in 139 cases of retinoblastoma are reviewed, together with the results of conservative treatment by radiotherapy, light coagulation, and cryotherapy. The indications for each method of treatment are discussed in the

light of these results and it would seem that these patients are best dealt with in centres where all these facilities are available.

(3) Although retinoblastoma is a malignant tumour, the prognosis for vision and for life with these methods of examination and treatment is more favourable than in former years.

We should like to thank Mr. H. B. Stallard for access to the records of some of these cases originally under his care, Prof. Barrie Jones in whose Department some of the patients were treated, and Miss Heather Payne for secretarial assistance.

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A new implant for glaucoma

Effect of removing implants

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A new type of draining implant and the results of 47 operations have been discussed by Molteno (1969a). This implant consists of a translimbal tube rigidly attached to, and opening onto the external surface of a thin circular acrylic plate 8 mm. in diameter. This plate is curved to fit and is sutured firmly to sclera. When covered by a flap of conjunctiva and Tenon's capsule the plate forms the floor of a uniocular bleb in free communication with the anterior chamber, which cannot shrink to an area less than that of the plate. These implants controlled the intraocular pressure in 83 per cent. of patients with medically uncontrollable glaucoma and in all nine patients who received systemic steroids to reduce bleb fibrosis. Several of the earlier cases developed excessively fibrosed blebs, and 32 per cent. of them needed long-term local steroid medication to prevent attacks of iridocyclitis.

The removal of implants was considered because, both in the rabbit and in man, a firm fibrous bleb formed around the implant so that it could be removed after a suitable lapse of time leaving both fistula and bleb intact.

This removal would avoid corneal complications from the presence of the plastic and inflammatory reaction at points of relative movement between eye and implant (Molteno, 1969b) which might be causing continuous deposition of fibrous tissue in the bleb wall. The blebs and fistulae left on removal could be expected to persist indefinitely since they would be lined by mature fibrous tissue which had already passed the stages of early contraction and late cicatrization (Walter and Israel, 1965), during which shrinkage had been forcibly prevented by the implants. Furthermore, the large diameter and unilocular nature of the blebs would result in a given intraocular pressure exerting a far larger force stretching the bleb wall than would be the case with a smaller bleb, since the force stretching the wall of a vesicle is equal to the pressure within multiplied by its radius of curvature (Young, 1805; Laplace, 1807).

The implants were accordingly removed from nineteen eyes. In three eyes (Cases 7 and 8) implants of Perspex were removed because they caused intractable uveitis; in one case a Stellon implant was removed because the bleb became overfibrosed and the glaucoma remained uncontrollable. In the remaining fifteen eyes, Stellon implants were removed in an attempt to improve adequate drainage and obviate the need for long-term local steroid medication. The surgical techniques used for removal and the results obtained are the subject of this communication.

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Design of clinical trial

Patients with advanced glaucoma, in whom the visual acuity had fallen to 6/60 or less, were admitted to hospital for full evaluation and a trial of medical therapy. Those in whom the intraocular pressure could not be reduced to 20 mm. Hg had implants inserted. In most cases they remained in hospital until the removal of the implants between 5 weeks and 7 months later. Those discharged from hospital were readmitted for evaluation of their condition before the implant was removed. After the removal they remained in hospital for between 6 weeks and one year, after which they were followed as outpatients.

Diagnosis and evaluation

All cases were examined by the author and underwent a full ophthalmic examination, including applanation tonometry, tonography, and gonioscopy.

The trial of medical therapy lasted at least 7 days. The following dosages were used:

(1) Diamox 250 mg. four times a day with potassium supplement

(2) Glycerol 150 ml. four times a day for up to 2 weeks

(3) Gutt. Epitrate 2 per cent. four times a day

(4) Gutt. Phospholine iodide 0·06–0·125 per cent. or, if tolerated, Gutt. Tosmelin 0·25–0·5 per cent.

Follow-up

During hospitalization, the patients were seen daily and had at least weekly slit-lamp examinations with applanation tonometry. At outpatient visits applanation tonometry and slit-lamp examination were routine and tonography was performed at longer intervals to confirm that the changes observed in the intraocular pressure were actually due to changes in outflow.

Methods used

The intraocular pressure was measured with a Goldmann applanation tonometer fitted to a Haag-Streit 900 slit lamp. Tonography was carried out for 4 minutes using a Schwartzer electronic tonometer with continuous strip recorder (both instruments were regularly checked using the calibration standards provided by the makers).

Surgical techniques

TIME OF OPERATION

It was soon discovered that at least 3 months' delay after the insertion of an implant was needed for a firm bleb to form. Removal before 3 months (Cases 5, 6, 7, 12, and 13) gave relatively poor results, while accurate watertight closure of the incision into the bleb was very difficult. Therefore most implants were removed between 3 and 7 months after insertion, but there was no technical advantage in waiting more than 4 months as they attained their greatest thickness by the end of the third month.

ANAESTHESIA AND HYPOTONY

General anaesthesia was preferred but when it was not available, local anaesthesia and akinesia were used as for a cataract extraction. Hypotony was produced either by intravenous infusion of 10 per cent. Mannitol solution or by the administration of 500 mg. Diamox and 150 ml. glycerol by mouth.

LIBRARY

STEPS IN SURGICAL TECHNIQUE

(1) Exposure of the bleb was provided by a speculum and a superior rectus stitch carefully inserted to avoid the bleb.

(2) A circumferential conjunctival incision was made 3 mm. behind the bleb and its limbal edge was retracted to expose the posterior edge of the bleb.

(3) After all bleeding points had been lightly cauterized a Bard-Parker knife was used to make a single clean incision into the bleb cavity. This incision was placed 1 mm. anterior to the posterior edge of the inner fibrous bleb and carried across the full width of the episcleral plate.

(4) The posterior stitch holding the implant to the sclera was cut and an iris repositor was used to ease the posterior edge of the episcleral plate away from the bleb cavity.

(5) The two anterior sutures holding the implant to the sclera were cut by sliding a Tooke's knife forward between the episcleral plate of the implant and the sclera. The implant was then grasped with a pair of toothed forceps and gently removed (Fig. 1).

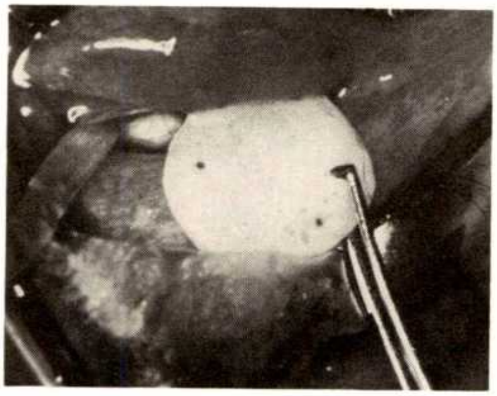

FIG. 1 *Removing implant from bleb*

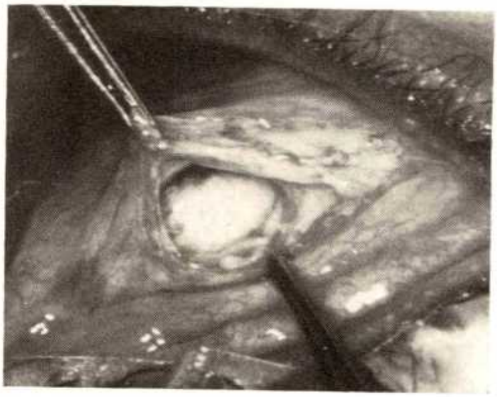

FIG. 2 *Bleb cavity lined by fibrous tissue.*

(6) A sliver of tissue comprising the full thickness of the bleb wall together with overlying conjunctiva was removed from the anterior lip of the incision, using curved scissors; a watertight closure of the inner fibrous layer of the bleb was then effected by five or six interrupted edge-to-edge sutures of 7·0 silk and the anterior chamber was re-formed by injecting a medium-sized air bubble into the bleb (Fig. 2).

(7) The conjunctiva was closed by a continuous suture of 7·0 silk and the operation was completed by the injection of Lincomycin with Depo-Medrol beneath the conjunctiva in the quadrant opposite the bleb.

During the removal of the implant the utmost care was taken to avoid stretching or otherwise injuring the inner fibrous layer of the bleb. In two cases, part of the bleb was lifted from the sclera, so demonstrating that the attachment of bleb to sclera formed a plane of weakness.

POSTOPERATIVE CARE

All eyes were single-padded for 24 hours, after which the patients were allowed up, wearing dark glasses. Gutt. Sofradex and gutt. Phenylephrine 10 per cent. were given until the eyes became quiet after 2 to 4 weeks. One patient (two eyes), a 15-year-old girl (Case 14), received systemic steroids for 4 months after the implants were removed in order to suppress fibrous tissue activity in the blebs. Two patients (three eyes) in whom Perspex implants excited a severe uveitis (Cases 7 and 8) received systemic steroids for 6 weeks and 7 months respectively after the removal of the implants.

OPERATIVE AND POSTOPERATIVE COMPLICATIONS

In this small series of nineteen operations for removal of implants no operative complications were encountered. The only postoperative complications occurred in Case 2 (two eyes) in whom malignant glaucoma developed 4 days and 7 months respectively after removal of the implants. The attacks occurred 3 days apart a week after the patient had finished a 7-day course of Orenzyme which had been given to determine whether it would improve drainage. In both eyes the glaucoma was successfully treated by withdrawing fluid posterior vitreous through a pars plana incision, combined with re-formation of the anterior chambers by means of air inserted through a single-thrust cyclodialysis. Both anterior chambers remained deep and drainage was re-established and has persisted in both eyes for a year since these episodes.

Results

BLEB BEHAVIOUR AFTER REMOVAL OF IMPLANT

In the immediate postoperative period, except for the three eyes in which Perspex implants had been used (Cases 7 and 8) the eyes remained quiet with a mild inflammatory reaction along the suture line. The blebs were all distended while the intraocular pressures rose within 10 days to the levels present immediately before removal of the particular implants. At this stage aqueous could easily be displaced from eye to bleb and *vice versa* (Fig. 5, below).

After 1 to 4 months, the blebs showed definite changes, either increasing in area with an associated fall in intraocular pressure or starting to shrink with an associated rise in intraocular pressure. (Bleb spread occurred in the eight patients aged 50 years or more when 3 or more months had passed between insertion and removal of implants (Table I)).

Table I *Results in eight patients over 50 years old (eleven eyes)*

Case No.	*Age (yrs)*	*Sex*	*Diagnosis*	+ or − 3 *mths before removal (months)*	*Total follow-up*	*Intraocular Pressure (mm. Hg)*	
						Before removal	*Final*
1	53	M	Primary glaucoma	+	19	23·1	8
2 R	79	M	Primary glaucoma	+ Malignant glaucoma	20	18·5	19
L	79	M	Primary glaucoma	+	25	37	20
3	78	M	Primary glaucoma	+	7	23	75
4	61	M	Primary glaucoma	+	4	24	16
5 R	65	M	Primary glaucoma	−	17	16·5	19
L	65	M	Glaucoma secondary to trauma	−	16	18	11
6	67	M	Primary glaucoma	−	22	17	22
7 R	53	M	Primary glaucoma	− Perspex Uveitis	20	28	12
L	53	M	Primary glaucoma	−	20	26	12
8	50	F	Primary glaucoma	+	6	32	25
Range	50–79				4–25	16·5–37	7·5–25
Mean	64				16	23·9	15·6

Bleb shrinkage occurred in six out of the eight eyes belonging to the six patients less than thirty years old, and in all cases in which the implants were removed before 3 months had elapsed (Table II).

Table II *Results in six patients under 30 years old (eight eyes)*

Case No.	*Age (yrs)*	*Sex*	*Diagnosis*	*+ or − 3 mths before removal*	*Total follow-up (mths)*	*Intraocular pressure (mm. Hg)*	
						Before removal	*Final*
9	25	F	Primary glaucoma	+	31	20	35
10	16	F	Glaucoma associated with Sturge Weber syndrome	+	29	26	38
11 R	4	F	Buphthalmos	+	19	14·6	43
L.	4	F	Buphthalmos	+	19	25·8	43
12	22	F	Primary glaucoma	—	12	25	20
13	29	M	Glaucoma secondary to old perforating injury	—	15	30	42·5
14 R	14	F	Primary glaucoma	+ Steroids	13	22	20
L.	14	F	Primary glaucoma	+ Steroids	13	22	15
Range	4–29				12–31	14·6–30	15–43
Mean	16				18·8	23·2	32

The only exceptions to the above rules were a 50-year-old woman (Case 8) with Perspex uveitis in whom bleb shrinkage occurred and two eyes in a 15-year-old girl (Case 14) who was given large doses of systemic steroids for 4 months and in whom both blebs extended in area.

BLEB SPREAD (Fig. 3)

Where this occurred, the sharply demarcated fibrosed and elevated bleb, which remained after removal of its contained implant, gradually flattened and spread posteriorly and circumferentially while becoming less fibrosed.

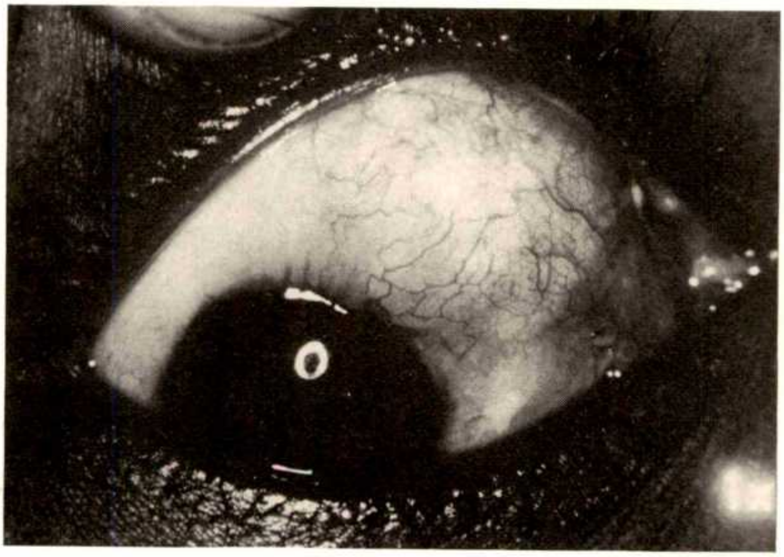

FIG. 3 *Bleb spread: Appearance of bleb 3 months after removal of implant*

Ultimately (after 1½ to 3 months) a large area, sometimes a whole quadrant, became covered by the bleb which consisted of well-vascularized but oedematous conjunctival and episcleral tissue. On massage of the globe this heaped up slightly and extended peripherally.

Gonioscopy of these eyes showed at first an open fistula where the translimbal tube had been but, by the end of the third month after removal, all those fistulae which could be clearly seen had become filled by a delicate network of fibrous tissue. During this period of spread, the intraocular pressure gradually fell to a stable level of between 7·5 and 20 mm. Hg approximately 3 months after the removal of the implant.

Drainage Routes Observed

In most cases in which the bleb had spread, the obvious oedema of the episcleral tissues suggested that most aqueous escaped from the bleb *via* the subconjunctival lymphatics. However, several blebs showed signs of transconjunctival drainage: both localized thin areas with a positive Seidel sign and diffuse areas where oedema of the episcleral tissues involved the conjunctiva so that numerous tiny microcysts formed in the epithelium on massage of the eyes. In two cases prominent aqueous veins formed in addition to the routes described above.

Although one of the blebs was found to be grossly overfibrosed on removal of the implant, all blebs which spread gradually lost their fibrosed walls and ultimately (after more than a year in one case) all signs of fibrous tissues having been laid down had vanished.

BLEB SHRINKAGE (Figs 4 to 7)

This occurred in all six patients less than 30 years old who did not receive systemic steroids. The sharply-defined, well-vascularized, fibrosed and heaped bleb which remained after removal of the implant remained unchanged for several weeks, and then slowly shrank over a period of up to 18 months to leave a small nubbin of heavily-fibrosed conjunctiva over the fistula. Gonioscopy showed that the fistula became filled with a tenuous network of fibrous tissue, which gradually became denser and ultimately consolidated to leave merely a dimple in the sclera to mark the site of the fistula.

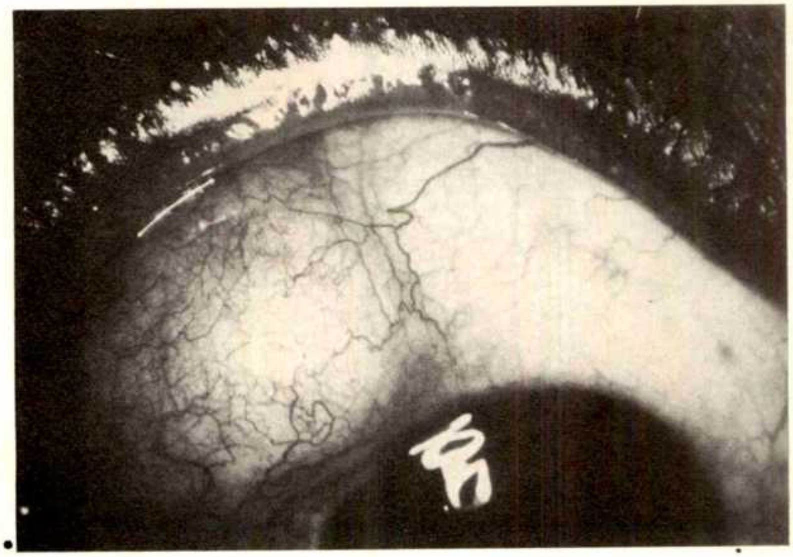

FIG. 4 *Bleb shrinkage: Appearance of bleb 4 months after insertion of implant and shortly before removal*

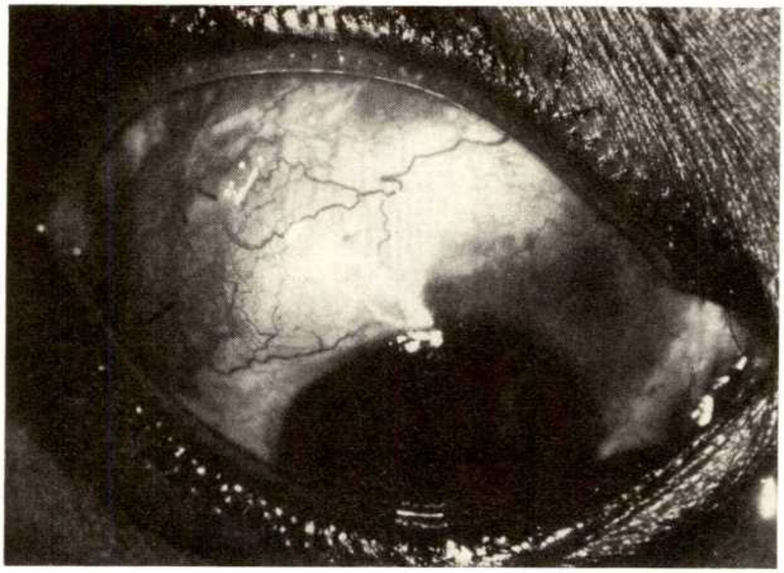

FIG. 5 *Same bleb as in Fig. 4, 1 week after removal of implant*

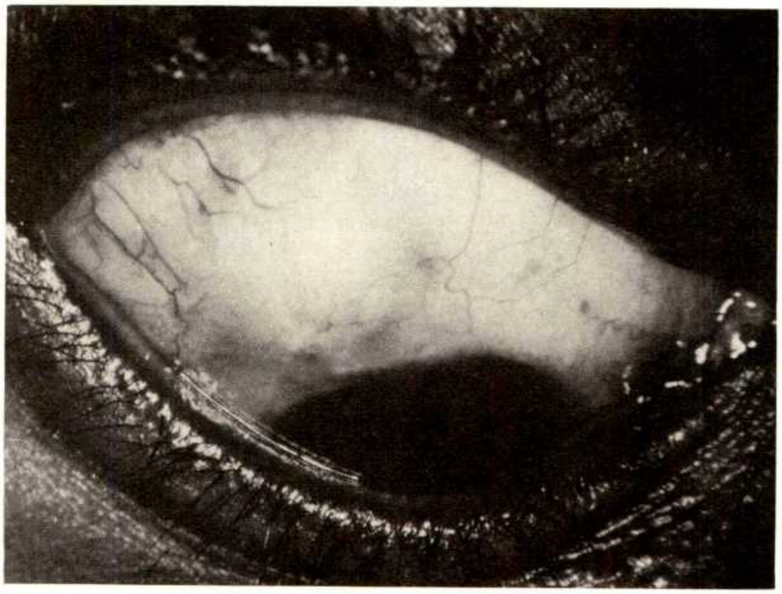

FIG. 6 *Same bleb as in Fig. 4, heavily fibrosed and shrinking 4 months later*

During the period of shrinkage, the intraocular pressure rose steadily until as the bleb disappeared the preoperative level was regained. Once all drainage had ceased the fibrosed nubbin became thinner and less fibrosed until it had reverted to the appearance of normal conjunctiva between 6 and 12 months later.

Drainage Routes Observed

Virtually no drainage of aqueous was observed from shrinking blebs, apart from a minimal amount of transconjunctival drainage over the fistulae when the blebs were almost obliterated and the intraocular pressure markedly raised.

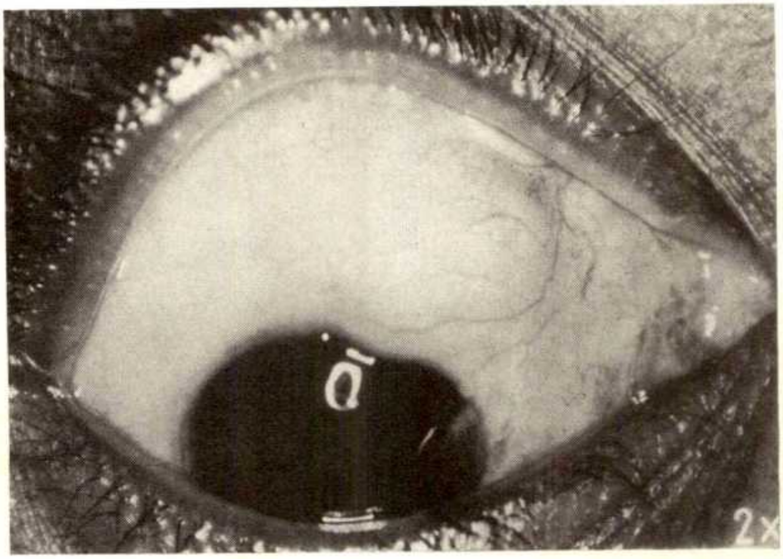

FIG. 7 *Same eye as in Figs 4 to 6, 27 months after removal of implant, showing reversion of bleb to normal conjunctiva. A second implant has been inserted in the nasal quadrant.*

In all cases except those with Perspex uveitis, the eyes remained quiet and by the fourth week after removal topical steroids and mydriatics were discontinued. One patient (Case 1) developed a mild iritis 10 months after removal of the implant; this was treated with steroid and cycloplegic drops, responded rapidly, and has remained quiet without medication during a further year of follow up.

EFFECT OF EARLY REMOVAL ON TENDENCY TO IRITIS

When implants were removed before the end of the third month, the behaviour of the eye varied according to the age of the patient. In those over 50 years old the blebs persisted but were smaller and less adequate than those which remained after the implants had been left *in situ* for 3 months or more.

In the group under 30 years old there were only two cases of early removal. In one the bleb became obliterated within 8 weeks of removal, and in the other rapid shrinkage occurred but the bleb "roof" became ischaemic and transconjunctival drainage was established and has persisted.

Discussion

In the elderly the effect of removing the implant was to maintain or reduce the pre-removal intraocular pressure and to eliminate the need for long-term steroid medication. Removal after 3 months uniformly resulted in a large, flat, thick-walled, moderately-vascular bleb, which extended in all directions on massage of the eye. This type of bleb is safe and permanent and always drains well (intraocular pressure 7·5–20 mm. Hg; C values 0·20–0·46).

In young patients removal, even when delayed for several months, resulted in a higher intraocular pressure in every case, except where systemic steroids were given to the limit of tolerance for 4 months after removal. Good drainage was obtained in this particular case, with flat extensible "permanent" type blebs, but it is not safe to give steroids in this manner as a routine.

Although the results are based on small numbers of cases, the effect of age on bleb behaviour was so marked that the removal of implants in patients less than 50 years old seems to be contraindicated. Young patients fortunately tolerate implants very well.

In the elderly, removal gives an ideal result, but the reason why there should be this marked difference between the age groups is not immediately obvious.

The overall results of insertion followed by removal were:

(1) Control of intraocular pressure without medication: twelve cases (9 over 50 years)
(2) Control of intraocular pressure with medication: one case (over 50 years)
(3) Failure: six cases (5 under 30 years).

POSSIBLE CAUSE OF BLEB SHRINKAGE IN THE YOUNG

The persistent vascularity and increasing fibrosis of shrinking blebs in young patients was associated with markedly raised intraocular pressures, but was followed by complete disappearance of the heavily-fibrosed bleb wall once all drainage of aqueous had ceased. This behaviour suggested that in these cases the aqueous exerted an irritant effect on the bleb wall. Epstein (1959) demonstrated histologically that the aqueous from an eye with absolute glaucoma had a fibrosing effect on the episcleral tissues, which caused failure of a seton operation in approximately 4 weeks. There is no direct evidence of the nature of the irritating factor, but ischaemia of any tissue results in the release of vasodilating factors while necrosis and autolysis of tissue releases factors which excite an acute inflammatory response followed later by fibrosis (Walter and Israel, 1965).

In these cases with nearly absolute glaucoma the pressure had been reduced by the initial insertion of the implant and in three cases in young patients the pressure had been below 30 mm. Hg for between 4 and 6 months, making it seem unlikely that tissue breakdown products from the intraocular structures would persist so long. However, in cases of rubeosis iridis, there is generally a lapse of several months between central vein occlusion and the onset of neovascularization. In this condition, a vasoformative factor produced by destruction of intraocular structures was postulated by Smith (1955, 1961), Ashton (1961), and Sanders (1961) as the cause of the neovascularization. The persistence of this factor months after the occlusion suggests that the "Epstein factor" could likewise persist for several months after normalization of the pressure and could be responsible for the fibrosis which obliterates the blebs, and that both factors have a common origin in destruction of intraocular tissue.

In older patients the glaucoma was equally advanced, but because aged tissues respond less actively to all stimuli the fibrosing response of the bleb walls was insufficient to raise the intraocular pressure or contract the blebs, and the blebs therefore remained until all tissue breakdown products had been eliminated, after which gradual loss of fibrous tissue occurred. The loss of fibrous tissue in these cases could be a manifestation of the degenerative action of normal aqueous on the episcleral tissues described by Teng, Chi, and Katzin (1959), but that it is not the only process leading to loss of collagen is shown by the defibrosis which occurred in shrunken blebs after all drainage of aqueous had ceased.

INDICATIONS FOR REMOVAL OF IMPLANTS

Since the initial publication of the results obtained by inserting implants (Molteno 1969a,b) the number of such operations has risen to eighty. The more recent cases have confirmed the value of systemic steroids in avoiding overfibrosis of the blebs and eliminating late postoperative iridocyclitis. Thus, at present, the author routinely inserts implants under steroid cover and leaves them in. Removal is helpful in elderly patients to whom systemic steroids cannot be given for medical reasons, in elderly patients who live so far away that supervision is impossible, and to forestall perforation of a bleb if the implant has been incorrectly inserted. If guided by these indications removal will increase the usefulness of implants and further improve the overall results.

Summary

(1) The theoretical advantages of removing the author's glaucoma implants after a suitable period are stated.

(2) The surgical techniques for removal are described and the results obtained in a series of nineteen removal operations are reported.

(3) The effect of the patient's age on the results is stressed and a possible causative mechanism discussed.

(4) The present indications for removing an implant are given.

I wish to thank Prof. M. H. Luntz for his help and encouragement. My thanks are due to the Superintendents of Baragwanath Hospital and St. John's Eye Hospital for their co-operation and assistance. This work was assisted by grants from the University of the Witwatersrand and the Council for Scientific and Industrial Research.

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Acquired unilateral loss of dark adaptation

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Poor dark adaptation is a not uncommon symptom and may occur in a wide variety of diseases but its occurrence in one eye only is far less frequent. When it occurs unilaterally, an obvious ocular disease is generally present to account for it and visual functions other than that of dark adaptation are also depressed. Some subjects with poor dark adaptation may have no demonstrable ocular lesion nor any other defect of visual function. Almost always they have one of the forms of congenital night blindness but sometimes the trouble is the first evidence of a progressive tapeto-retinal degeneration. Electrophysiological studies of the retinal function of these patients have proved to be useful, and Armington and Schwab (1954) have shown that by using electroretinography patients with a non-progressive night blindness can be differentiated from those with a progressive tapeto-retinal degeneration. Auerbach, Godel, and Rowe (1969) have similarly studied a large series of patients with night blindness. They have shown that patients with an apparently stationary night blindness fall into two main groups, but they also note that progression of the condition may occur. An acquired form of night blindness without obvious ocular defects and without disturbance of any other ocular function was described by Kelsey and Arden (1969) in which electrophysiological tests of retinal function suggested a lesion at the level of the bipolar cell layer. Two patients with similar acquired changes which were strictly uniocular are described below.

Methods

Dark adaptometry was done using a Goldmann-Weekers Dark Adaptometer. Electro-oculography (EOG) was based on the technique described by Arden, Barrada, and Kelsey (1962), and electroretinography (ERG) was carried out in a manner similar to that described by Karpe (1945). The details of the methods have been described previously by Kelsey and Arden (1969).

Case reports

(1) *A man aged* 48 (MED 620) had complained of gradually worsening vision of the right eye for several months.

EXAMINATION

The unaided visual acuity was 6/12 in the right eye and 6/18 in the left. The refractive error was not determined but no ocular abnormality could be found. A tentative diagnosis of tobacco amblyopia was made and the patient was referred to the Electrodiagnostic Clinic for further investigation before a more detailed clinical evaluation was carried out.

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When he was seen in the Electrodiagnostic Clinic the visual fields were determined using a Goldmann Projection Perimeter. The left peripheral field was found to be full but there was a slight generalized constriction of the right field. No scotoma indicative of tobacco amblyopia could be found. The results of the other tests are shown in Fig. 1.

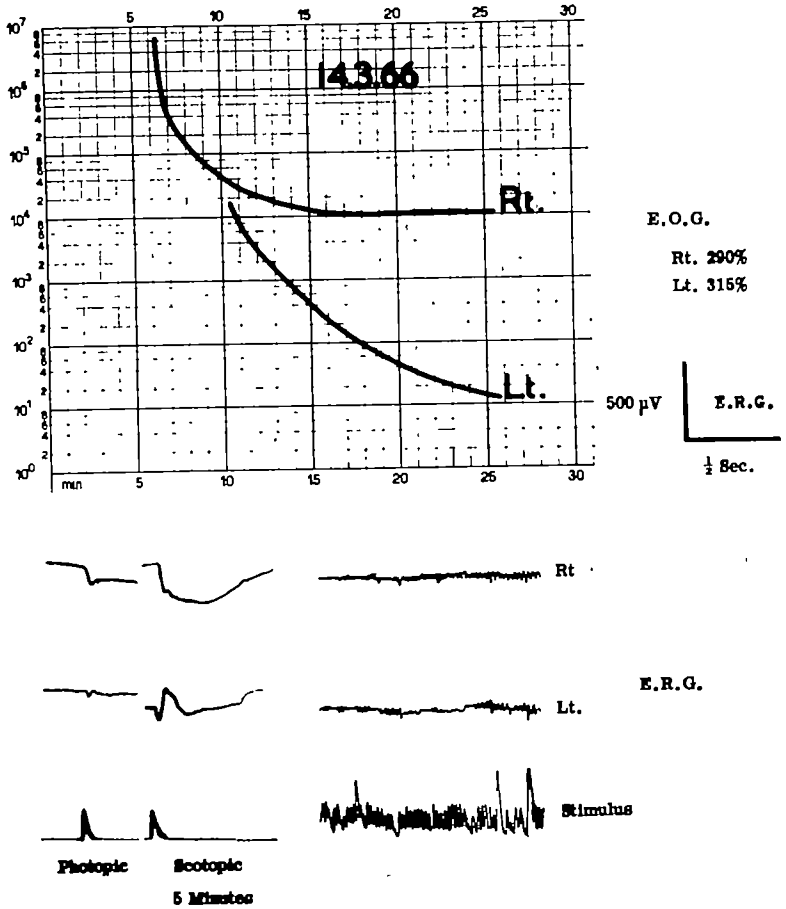

FIG. 1 *For full description see text*

Dark adaptometry confirmed that the vision in the right eye was abnormal in that a scotopic phase was absent while the left eye had a normal curve. The EOG showed a normal response in both eyes with a light rise of 290 per cent. from the right eye and of 315 per cent. from the left eye. The left ERG was normal. The right ERG was abnormal in that only a negative potential was recorded which returned to the baseline after 0·5 to 1 second. The flicker fusion rate of the two eyes was normal.

After these tests the patient failed to return to the outpatient clinic and postal enquiry has failed to elicit his whereabouts.

(2) *A married lady aged* 50 (MED 1141) in good health had had no eye trouble before the onset of her present complaint. One night she awoke and noticed that the vision of the right eye was abnormal. The bedroom was dimly lit by a light outside, and with her left eye she was able to discern the objects in the room but with her right eye she could see none of them. With the right eye she could see the light outside but it seemed to have an orange hue. Enquiry revealed no

possible precipitating cause of this visual change. She was on no systemic medication and the only unusual recent event had been that she had cleaned a boat with an organic solvent a day or so previously.

EXAMINATION

No ocular abnormality could be found on clinical examination. There was a minimal refractive error and the visual acuity was 6/6 in each eye. The ocular media were clear and apart from a non-specific pigmentary mottling of the periphery the fundi were normal. The visual fields to 3/300 on the Lister perimeter and 2/2,000 red and white on the Bjerrum screen were full and equal in the two eyes.

The patient was seen in the Electrodiagnostic Clinic on July 27, 1967, and the results are shown in Fig. 2. The subjective change in dark adaptation was confirmed by the absence of a scotopic phase in the right eye while the left eye had a normal curve. The EOG of the left eye had a normal light rise of 200 per cent., but that of the right eye was subnormal at 145 per cent. The ERG of the left eye was normal but that of the right eye had a negative deflection only. The flicker fusion response was technically unsatisfactory but no abnormality was evident in either eye.

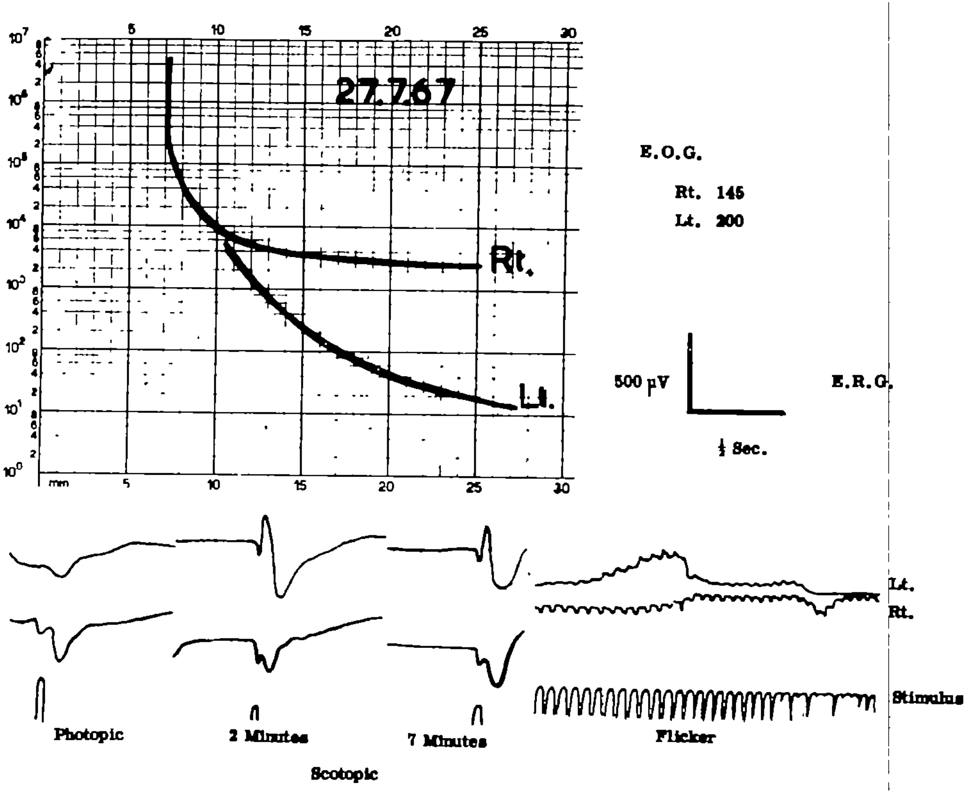

FIG. 2 *For full description see text*

The patient's condition remained unchanged for 4 months when she reported that the vision of the right eye had returned suddenly to normal. The electrodiagnostic tests were repeated on November 9, 1967, and the results shown in Fig. 3 (opposite) confirmed the symptomatic recovery. All the results were normal and equal in the two eyes.

Enquiry 2 years later has revealed that the condition has not recurred.

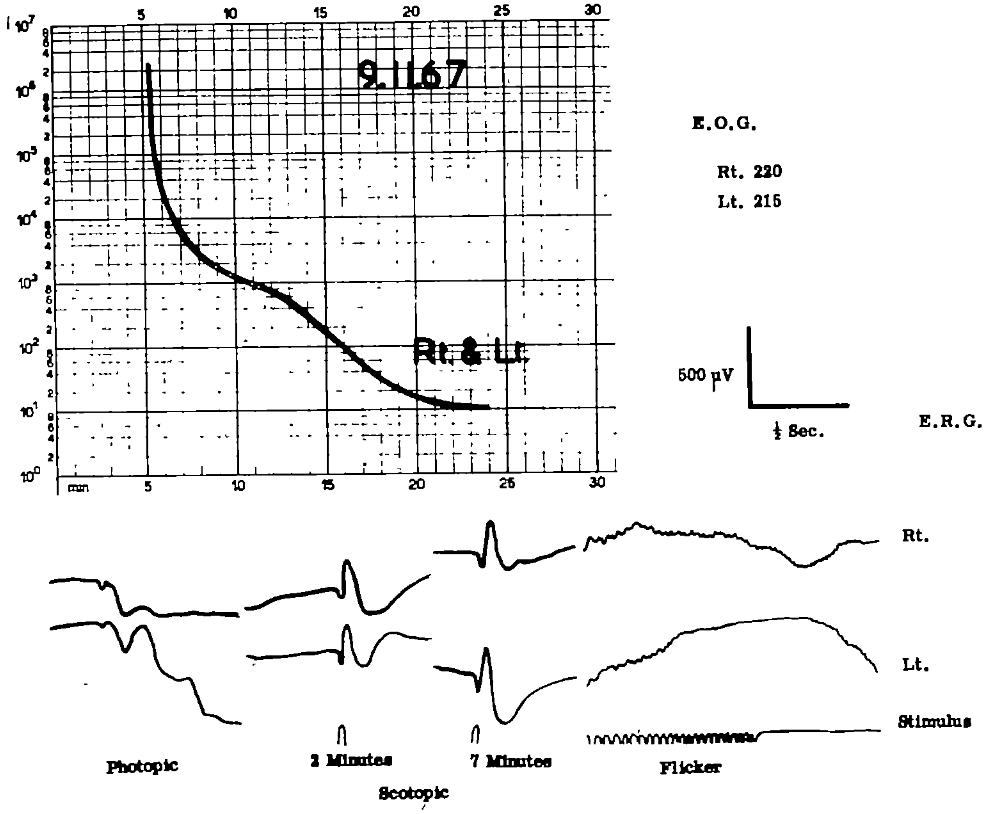

FIG. 3 *For full description see text*

Discussion

The mechanism of dark adaptation is still uncertain, but Arden and Weale (1954) have demonstrated that a nervous process is involved and Dowling (1967) has suggested that this process occurs at the level of the bipolar cells. Thus the use of both the EOG and the ERG might be expected to be of use in the investigation of abnormalities of dark adaptation, as it is probable that the EOG arises from the external retinal layers (Arden and Kelsey, 1962) while the ERG has a contribution from the bipolar cell layer (Brown, 1966).

Animal studies cannot be expected to show the relation of electrophysiological changes to dark adaptation as the visual function is highly subjective, but two papers are relevant to this discussion. Cone and Ebrey (1965) occluded the central retinal artery of the rat and produced an ERG of the receptor potential waveform similar to that of the patients described. Unlike our patients the flicker fusion of the receptor potential of the rat was abnormal in that it failed to follow a stimulus that could be followed by the ERG of the intact rat.

It seems unlikely that the lesion causing the trouble in our patients is equivalent to a blockage of the central retinal artery. This supposition is supported by the findings of Gouras and Carr (1965), who occluded the central retinal artery of the monkey. Here again a receptor potential type of ERG was produced, but it was noted also that the EOG was lost. This the authors took as evidence against the theory of the origin of the EOG from the outer layers of the retina and they suggested that it must arise from a level similar to that of the ERG *b*-wave. Clinical evidence in humans and the histological preparations of the authors show that the effect of the central retinal artery block is not confined to its level of supply and an externally originating EOG could easily be disturbed.

Several cases of central retinal artery occlusion have been seen in this clinic. The patients have usually been in the acute phase of the condition, and it was found that both the EOG and the ERG were grossly deranged. This may be expected both from the extensive retinal disturbance seen ophthalmoscopically which gives a picture quite unlike that found in our patients and from the possibility that the block also affects the choroidal circulation. One patient with an optic atrophy due to an old retinal artery occlusion has been seen in the clinic who had the typical negative ERG in the affected eye with a normal ERG in the unaffected eye and a normal EOG in both eyes. Unfortunately this patient was seen in the early days of the clinic and the flicker fusion test was not performed. That the dark adaptation was not tested was probably due to the fact that the visual acuity in this case was perception of light.

Clinical studies of night-blind patients using both the ERG and the EOG have been infrequent. Carr, Ripps, Siegel, and Weale (1966) described a night-blind female who had been shown to have a normal retinal concentration of rhodopsin. She had a negative ERG and the authors suggested that the abnormality causing the poor night vision lay at the level of the bipolar cells. She had a low EOG and in the presence of a normal retinal concentration of rhodopsin it was considered that the EOG could not arise in the external retinal layers. Like Gouras and Carr (1965) these authors proposed an origin proximal to the retinal receptors. This may not be a valid proposal as their patient was short-sighted and it has been shown that myopes tend to have a low EOG (Barrada and Kelsey, 1964).

There is therefore good evidence that poor night vision may be caused by a defect at the level of the bipolar cell layer. It is probable that there are several causes for this, giving rise to congenital, juvenile acquired, and adult acquired forms. Furthermore, it seems that irreversible cell damage may not occur as recovery can take place. The change in the EOG in the night-blind period of the patient who recovered is difficult to explain, and it is unfortunate that this test was not done at intervals while she was affected by night blindness. The first test was done at the onset of the condition. Experience in this clinic has shown that the EOG is the most sensitive of all the electrophysiological tests to any generalized retinal abnormality and the result may be merely an expression of this general rule. Arden (1968) has also suggested that a change in the EOG may take place because of a lesion of the more proximal retinal layers without the EOG generator being directly affected.

Whatever the cause of the condition it is evident that one or more nosological entities have been revealed by the combined use of these two tests of retinal function. Furthermore, the condition may not be rare. From the first 2,000 patients seen in the Electrodiagnostic Clinic, six had the bilateral acquired form and two the adult unilateral form. An awareness of the existence of the condition will doubtless reveal many more cases.

Summary

Two cases of unilateral loss of dark adaptation in adult life with no obvious ocular disease are described. The results of the EOG and ERG suggest that the cause is a generalized lesion of the bipolar cell layer and that the condition may be reversible.

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Testing visual acuity

(1) A legible four-position test object for standardization of measurement

(2) A new approach to the design of test letters for clinical examinations

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Measuring visual acuity in practical fields is far from satisfactory. Test types are of major importance and in this field there is need for research. I have developed a legible four-position test type, for measurements where standardization is most important, and a principle for the design of test letters, for examination and measurement. The four-position test type is derived from the clear preference for legible test types in practical work, searching for a compromise between letters and the classical Landolt ring, or the Snellen illiterate E. This may be considered for standardization in the field of official measurements. From these rotating test types I then developed the idea of a new approach to letter design for clinical testing (that is, for more rapid non-official examinations) based on square two-position patterns. These two proposals have different purposes and are dealt with separately below.

(1) Legible four-position test object

An operative decision of the International Civil Aviation Organization (1962), an inter-governmental institution, administering international law, recommends: "... optotypes of Landolt, or similar optotypes ..." for assessing visual requirements for personnel licensing. When the civil aviation standards were already official, the International Federation of Ophthalmological Societies decided in relation to other transport workers: "As optotypes shall be used letters". These two decisions are not standardizations, being limited to these words.

Two important national decisions were successively reached on the selection of letters for visual acuity measurements. In 1959 a Subcommittee of the A.M.A. Committee on Optics and Visual Physiology (Sloan, 1959) approved the charts developed at the Wilmer Institute in Boston. Test types of these charts are:

5 × 5 non-serif letters **C D H K N O R S V Z**

In 1968 a British Standard on Specifications for Test Charts was approved by the Ophthalmic Standards Committee. For this the style and selection of letters are:

5 × 4 non-serif letters **D E F H N P R U V Z**

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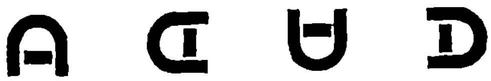
The difference between these two resolutions presents another obstacle to an international standard based on letters. A choice of letters based on statistics of legibility or on previously-existing charts is subject to differences which may be marked in different peoples or countries.

It may thus be possible to create a standard of official measurements by a compromise between letters and rotating test objects, i.e. a four-position test type legible as four letters. A single test object has many practical advantages in standardization, apart from the theoretical advantage that it is a better unit of measurement than a group of letters with casually different patterns (selected on statistics of legibility). The rotating test type I propose is shown in the four positions in Fig. 1.



This test type can be described as a half-ring measuring one-fifth of the outer diameter in thickness, continued by two parallel bars, as thick as the ring and half as long as the diameter; these parallel bars embrace a perpendicular bar, equal in thickness, and separated from them by two spaces one-third of its thickness; the distance of this bar from the line determined by the ends of the two outer bars is equal to its own thickness.

The relative dimensions of this pattern are clear, except for those separating the inner bar. This separation is not intended to be a critical detail: it is necessary for the sign to be accepted as C and U, at the beginning of the examination, and it must be small for the readings of A and D. The dimension I have adopted is enough for the purpose and is compatible with typographical reproduction.

In my experience, subjects of the age and education of transport operators immediately recognize the four letters in this pattern, after they are shown and named at the beginning of the examination, well above the threshold of recognition. This is a practical advantage over the Landolt ring; another advantage that assists standardization, is that there are clearly four positions, and not four or eight or more. In the theoretical field it has to be noted that the minimum separability is not emphasized by this pattern on the overall design and dimensions, which are the characteristics of test objects which must be known to be recognized.

A four-position test type has many advantages for standardization over a group of test letters. It is easier to reach agreement on a single pattern than on eight or ten; there is no alternative between the 5 × 5 or 5 × 4 dimensions; the possibilities of selection from among similarly-designed test types are very few; such tests measure retinal factors of resolution much better than a group of letters necessarily selected for their relative legibility.

The pattern I propose has, moreover, some advantages over illiterate E's: there are more clues for recognition, so that the effect of astigmatism is less marked; and there is just one pattern against the four E's which have historical importance (Snellen's 4/5 inner bar; Pfluger's 3·5/5; Pergens' 5/5; Ammon's 5/5 and truncated corners).

When the visual acuity is examined with the customary charts, with many rows of test types, four possible answers only are not enough to permit recognition at a glance when the subject is reading. But for official examinations such charts are not to be recommended, because they can be memorized. For official assessment of public law requirements, the time factor in giving the test must not be a decisive one.

(2) Design of test letters

The history of the style and selection of letters for testing visual acuity was summarized by Bennett (1965). It may be put in a few words as follows:

Snellen (1862) and Armaignac (1906) using letters with serifs; Monoyer (1875) and Sulzer (1904) using letters without serifs, adopted practically all the alphabet;

In 1868 Snellen limited the letters to fifteen;

A stricter selection was made by Green (11 letters in 1868, but 16 in 1872);

Oliver (1885) and Cowan (1928) used seven and nine letters respectively to conform to the minimum separability principle;

Hay (1919), Blaskovics (1923), and Sloan (1959) used eight to ten letters which they found of equal legibility (many other authors have experimented on legibility but I have not found charts published by them);

Emsley (1933) and Finkel (1963) used letters and groups intended to help with refracting.

In this scheme (very shortly, as the charts published by their authors run into hundreds) three lines of development may be traced:

(1) Design of the letters to be discriminated by clues one-fifth of the overall size;

(2) Selection for equal recognition;

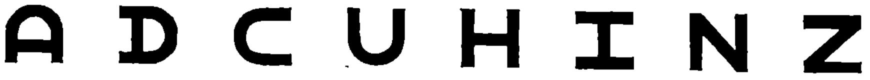
(3) Interest in refracting greater than in measuring.

A new development is possible derived from the rotating test types used to test illiterates and in research.

In visual acuity testing, letters are used for convenience, to save time: visual acuity should not measure the subjects ability to interpret alphabets imperfectly focused or badly transmitted by the retina and nerve fibres: what matters in a visual acuity test object is its ability as a geometrical pattern, to test refractive or retinal functions. The minimum separability requirement as applied by Snellen to letters has failed to ensure sufficient uniformity of response and has now been abandoned. A quotient of legibility within a certain interval is a necessity, but it varies with the individual and is closely related to subjective functions. We could then design letters for their geometrical properties. A few simple patterns would at least give a purer test of retinal resolution. If this lead to a wider range of statistical legibility, it would be an advantage in the clinical evaluation of the functions of the eye and could be overcome in measurements by appropriate methods of scoring.

Interesting geometrical properties can be obtained to extend to letters the principle of rotating patterns, which has a long history in the illiterate E and in Landolt's ring. At least half the alphabet may be so designed that one letter transforms into another by rotation through 90°. Among these letters we can use those whose patterns are most useful for refracting or for clinical measurements. Since the optical system of the eye has directional properties, two-position patterns would be better than the customary letters designed only on the minimum separability principle or selected on statistics of legibility.

The following couples of two-position letters are mostly derived from letters already used as optotypes (some of them are shown in Fig. 2):



AD, from Snellen's D: many reproductions in Bennett (1965, p. 239) and in Pergens (1906a, b).

CU, from the U of Green (1868) (see Pergens, 1906b, p. 133).

EM, from the E of Snellen or Pergens or Ammon (or EW from Pergens' or Ammon); reproductions in Bennett (1965), Ewing (1928), and Pergens (1907, p. 298).

HI, from Hay's H (see Bennett, 1965); the resulting I has very long serifs, but when well focused it is promptly identifiable.

KY, from a suitable K, designed with symmetrical oblique bars; these letters seem to me sufficiently identifiable (though there is no K or Y in the Italian alphabet).

NZ, from a suitable N (Hay's?, style and size in Bennett, 1965, p. 243).

These patterns are sufficiently numerous to permit different selections according to the needs of a particular clinic. There are straight and curved contours and different oblique lines. Some patterns are simpler, others more complicated; the relative proportions of black and white vary. Charts could be developed which are the best for refracting; moreover, since they will contain few patterns, the level of acuity will be more accurately measured. The patterns will be fewer than in any other set of letters numerous enough to be practical, as they contain half the number of letters. In consequence any set selected from them is a more exact unit of measurement. It will also be feasible to develop charts in which a selection of one or two patterns (two or four letters) repeated in each row is conventionally devoted to acuity assessment. In clinical tests a strict standardization would not be so necessary as in official tests, but it is desirable that the premises for it exist. Reducing the number of patterns is the only way to standardize, even in clinical examinations of the visual acuity. Also, for rotating patterns there is no alternative in relative dimensions, for the 5 × 5 size is enforced.

Summary

1. Official recommendations on visual acuity measurements are conflicting and/or inadequate. For international standardization a four-position test type which can be read as the letters ACDU is described. Its advantages over groups of letters, Landolt's ring, and illiterate E's are set forth.

2. The development of the selection of letters for acuity charts is traced. A new line is suggested, based on the overall geometrical pattern of a few letters, legible in two ways when rotated through 90°. Possible letters are listed. Their advantages for standardization in clinical tests are given.

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Flat anterior chamber and choroidal detachment in aphakia

Study of 500 cataract extractions

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This study was undertaken to find out the incidence of shallow anterior chamber and choroidal detachment after cataract extraction and to examine the relationship between these two relatively frequent postoperative complications.

Küchle (1962) had 10 per cent. choroidal detachments in the second postoperative week. In a series of 1,256 cataract extractions studied by Castrén (1960), the incidence of choroidal detachment was 10 per cent. in intracapsular and 3 per cent. in extracapsular operations; the difference was probably due to the difficulty of viewing the fundus in the latter. Choroidal detachments occurred from the 4th to the 56th postoperative day and healed with conservative treatment in all but one case. Most of these detachments were located nasally and inferiorly. Castrén did not mention the condition of the anterior chamber.

Bégué (1961) put the incidence of choroidal detachments at about 6 per cent. Voisin and Juge (1956) pointed out that many choroidal detachments existed with re-formed anterior chambers. Solares-Zamora (1964) observed that late loss of the anterior chamber occurred in 2 to 24 per cent., and that in many cases choroidal detachment accompanied the flat anterior chamber, but he did not state whether the one preceded or followed the other.

Postoperative loss of the anterior chamber without choroidal detachment may be due to wound leakage, synechiae of the pupil with the vitreous, or an abnormal collection of aqueous behind the anterior hyaloid membrane or forming pockets in the vitreous posteriorly.

Schepens (1961) thought that the capillary bed in some eyes could not withstand the sudden fall in pressure when the eye was opened, with the result that fluid collected in the subchoroidal space so causing detachment of the choroid. Bégué (1961) thought that the hypertonicity of the tissue was due to a disequilibrium of liquid in relation to the aqueous humour.

Present investigations

500 cases of senile cataract were studied. Preoperatively the patients received Tab. Dial 50 mg. on the previous night. The pupils were dilated with Homatropine eye drops half hourly from 6 to 7.30 am. on the morning of the operation, and pethidine and phenergan were given intramuscularly about 30 minutes before the operation. All were operated upon under local anaesthesia and by the same operative technique. Three to five Barraquer virgin silk sutures were used for wound closure. All were examined with the

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slit lamp at the time of discharge, and at each subsequent follow-up visit. In doubtful cases, the intraocular pressure was measured with a Schiötz tonometer 15 days after operation.

An analysis of the results shows that, out of 500 cases, thirteen (2·6 per cent.) had choroidal detachment and 37 (13·5 per cent.) had flat anterior chamber during the postoperative period. Four cases of choroidal detachment had normal anterior chambers. In three of the other nine cases the choroidal detachments appeared before the clinically shallow chamber was observed and healed after the chamber had re-formed. In five cases the chamber became flat first, and in one the two events were simultaneous. The detachment disappeared after the chamber re-formed in four of the last six cases. In the 37 cases of shallow anterior chamber the condition appeared at times varying from the fourth to the 75th postoperative day. Eight of these patients also had choroidal detachment; four had an obvious pupil block caused by vitreous, and in four there was a large vitreous mushroom almost touching the cornea.

The low ocular tension returned to normal when the chamber had re-formed. In four cases the tension was found to be higher when the chamber was shallow.

In three cases the anterior chamber re-formed after being flat for a few days, again became flat, and later re-formed again.

Surgical intervention was required in only one patient. The rest were all treated conservatively.

Summary

In 500 cases of cataract extraction the incidence of choroidal detachment was 2·6 per cent. and that of shallow anterior chamber was 13·5 per cent., and there was no regular relationship between the two conditions. The eyes were treated conservatively and these complications did not affect the ultimate visual acuity or intraocular pressure.

I am grateful to Dr. P. B. Banaji, Prof. of Ophthalmology, J. J. Hospital, Bombay, for his help in preparing this paper.

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Acute keratoconus in mongols

DERMOT PIERSE AND PETER EUSTACE

Croydon Eye Unit

Acute keratoconus is the term applied to the sudden development of a gross degree of corneal oedema in a patient with a pre-existing keratoconus. This rare condition was probably first described by Terrien (1906). An association between mongolism and acute keratoconus has recently been observed, the first two cases having been reported by Hoffmann (1956). Three cases (two bilateral) are reported below.

Case reports

Case 1, a 17-year-old low-grade mongol boy, was seen at the Croydon Eye Unit on July 29, 1959. His right eye had been red and photophobic for 3 weeks.

Examination

It was not possible to assess the visual acuity. The right eye was hyperaemic and the cornea was thickened, opaque, and oedematous, bulging forward in a globular fashion. The left eye showed early keratoconus.

Treatment

This consisted initially of gutt. atropine 1 per cent. twice daily and a firm pad and bandage. On August 12, 1959, since there had been no substantial change, the main intracorneal bulla was punctured and gutt. hydrocortisone 2-hrly was started. By August 19, 1959 (Figs 1, 2, 3, opposite) an improvement was apparent.

Course

On August 30, 1959, he attended again as an emergency having developed a similar acute keratoconus in the left eye. This eye also was treated with gutt. hydrocortisone 2-hrly and by September 23, 1959, it had virtually recovered.

After 6 weeks the patient was discovered to have a spontaneously-sealed left corneal perforation. A 5 mm. penetrating keratoplasty was carried out on March 13, 1960, but this, although initially clear, subsequently became opaque and vascularized.

Termination

The patient died suddenly at home on April 26, 1962.

Case 2, a 21-year-old mongoloid boy, presented at the Croydon Eye Unit on July 31, 1961. His right eye had been red and photophobic for 9 days.

Examination

It was difficult to assess visual acuity because of lack of co-operation. The right eye was hyperaemic and the right cornea, in about its central two-thirds, was thickened and oedematous, protruding forward in a cone. The left eye showed early signs of keratoconus.

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(1)

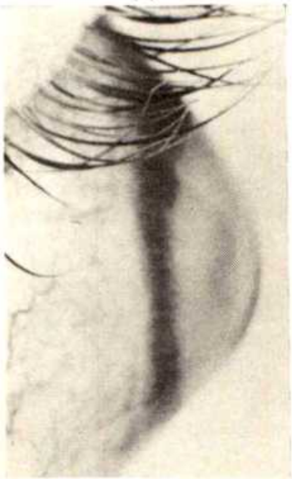

FIG. 1 *Case* 1. *Lateral view of right eye* 3 *weeks after onset of keratoconus.*

(2)

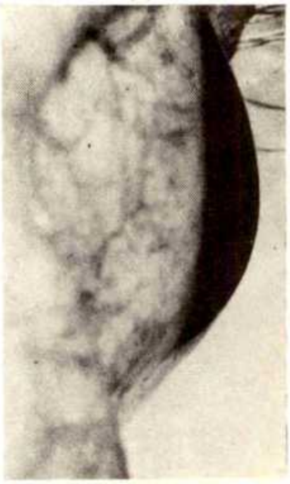

FIG. 2 *Case* 1. *Lateral view of right eye* 2 *weeks later.*

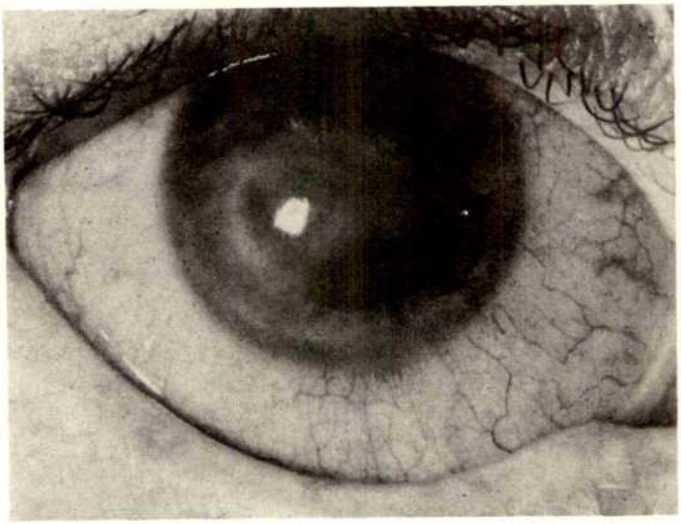

FIG. 3 *Case* 1. *Anterior view of right eye also* 5 *weeks after onset.*

Treatment

The affected eye was treated with gutt. atropine 1 per cent. once daily, oculentum chloromycetin once daily, and firm bandaging.

Result

By August 16, 1961, the oedema had almost resolved and when he was last seen on March 10, 1962, the corneae were almost of normal thickness with only slight evidence of keratoconus. There was a small linear superficial scar in the right cornea.

Follow-up

At this time the patient is alive and well and has had no further ocular trouble.

Case 3, a 27-year-old mongol girl, presented at the Croydon Eye Unit on February 22, 1962, with a 4-day history of pain and redness of the left eye.

Examination

The visual acuity appeared very reduced. The right eye was hyperaemic and the cornea was thickened and oedematous, bulging in a globular fashion. The left eye showed some signs of keratoconus, particularly prominence of corneal nerves, vertical linear striations in the stroma, and a slight coning of the cornea infero-nasally.

Treatment

Initially this comprised gutt. atropine 1 per cent. twice daily and gutt. Predsol 2-hrly, with a firm pad and bandage.

Result

By April 18, 1962, only a small linear stromal opacity and a very slight degree of keratoconus remained.

Course

Subsequently she was seen every 6 months and both corneae have remained healthy with a slight degree of keratoconus, the visual acuity with a myopic correction being approximately the same as it was before the acute episode. After 8 years, however, on January 3, 1970, she again attended as an emergency with a history that her right eye had been red and irritable for the past week. The eye was red and watering and a greyish, thickened cornea was bulging in a globular fashion with considerable corneal oedema. Treatment was started with oculentum Betnesol-N four times a day. For the next 7 weeks there was very little clinical change, but quite suddenly the oedema started to disappear rapidly. There is now only a slight degree of central corneal oedema and the cornea does not appear to be unduly thinned.

Discussion

Acute keratoconus presents as a photophobic watering red eye of relatively acute onset. Visual acuity is greatly reduced. The conjunctiva is hyperaemic. The cornea is cloudy grey, protruding in a globular fashion, and is seen to be greatly thickened with oedema. Often there are large bullae in the stroma and beneath the epithelium, so that the term "acute corneal hydrops" is perhaps more appropriate. Some degree of keratoconus is usual in the other eye.

The development of an acute episode is a rare complication of keratoconus in the normal individual and occurs much more frequently as a complication of keratoconus in mongols and those with other forms of mental deficiency. In 52 cases of acute keratoconus collected from the literature by Appelmans, Michiels, Nelis and Massa (1961), seven were mentally defective and ten were mongoloid. Eye rubbing has been blamed (Ridley, 1961; Cashell, 1962), and other conditions in which eye rubbing is a prominent symptom are known to be associated with keratoconus. Bietti and Ferraboschi (1958) proved the statistical relationship with vernal catarrh, and atopic eczema was shown to be associated with keratoconus by Brunsting, Reed, and Bair (1955). Since Hoffmann (1956) described the first two cases of acute keratoconus in mongols, many other reports have appeared (Leffertstra, 1959; Wilde, 1959; Woillez and Dansaut, 1960; Appelmans and others, 1961; Stanković and Biga, 1961; Kalt, 1962; Grayson, 1963; Dienstbier, 1965; Sédan, 1966). A series of eight cases was discussed by Slusher, Laisbon, and Mulberger (1968). The syndrome of mongolism is now known to be caused by chromosomal aberrations, of which three types have been found: trisomy of chromosome 21 (Lejeune, Gauthier, and Turpin, 1959), reciprocal translocation, one of the 13–15 group being attached to the extra chromosome 21 (Polani, Briggs, Ford, Clarke, and Berg, 1960), and mosaicism, the abnormal cells with trisomy 21 (Clarke, Edwards, and Smallpeice, 1961).

The following ocular features of mongols were listed by Skeller and Öster (1951) in a review of 81 patients: an upward, outward slope of the palpebral aperture 71 per cent., epicanthus 21 per cent., blepharoconjunctivitis 67 per cent., blue or grey iris 88 per cent., Brushfield's spots 86 per cent., lens opacities 46 per cent., convergent strabismus 31 per cent., keratoconus 6 per cent., divergent strabismus 3 per cent., and nystagmus 1·7 per cent. This incidence of keratoconus is in accord with that found by other workers (Woillez and Dansaut, 1960; Cullen and Butler, 1963), and is very much greater than in the general population (1/40,000—Jonkers, 1950). Rados (1948), who first reported the association of mongolism and keratoconus, quoted Geyer (1939) as having described two similar cases. It seems likely that a dystrophic process involves the epithelium of the cornea and probably also the lens. Histopathological examination shows that the essential changes in early keratoconus are confined to the basal layers of the epithelium and this was well demonstrated by the electron microscopic studies of Teng (1963). In its early stages he found fragmentation of the basement membrane with fibrillation, breaks in Bowman's membrane, and death of basal epithelial cells. He postulated the release of proteolytic and autolytic enzymes from the dead epithelial cells which affect the substance of the stroma leading to loss of collagen. Eventually breaks occur in Descemet's membrane and the endothelium, leading to the development of acute corneal oedema. Eye rubbing could lead to an increased release of these enzymes and thus be an important factor in the development of acute keratoconus.

That rupture of Descemet's membrane and damage to the endothelium is the essential explanation for the sudden development of corneal oedema was first suggested by Terrien (1906); it is now widely accepted, and there has since been ample histological confirmation (Böke and Conrads, 1957; Günther, 1958; Zajácz, 1963; Blodi and Braley, 1967). Wolter, Henderson, and Clahassey (1968) described a case in which three acute attacks had been observed to correlate with splits in Descemet's membrane. When the cornea was examined microscopically these splits were revealed by rolled edges with newly-formed membranes between. The newly-formed membranes differed in thickness, suggesting deposition at different times. However, it is common clinical experience that not all splits in Descemet's membrane (such as those that follow unintentional damage during surgery) produce corneal oedema. It would seem reasonable that there must be some additional factor, perhaps previous damage to the collagen of the stroma produced by autolytic enzymes. Experimentally this possibility was supported by Straub, Sautter, and Velten (1958), who were unable to produce corneal oedema after causing splits in Descemet's membrane in rabbits, whereas Appelmans and others (1961) produced a picture resembling acute keratoconus after the intracorneal injection of chymotrypsin, a proteolytic enzyme.

Acute keratoconus is essentially a self-limiting condition; thus treatment needs only to be supportive and should consist of padding the eye as a protective measure and probably the topical use of a steroid-antibiotic preparation. Keratoplasty does not seem to be indicated in the acute phase and is only subsequently advisable if the cornea becomes grossly thinned or the patient's visual requirements demand it; corneal grafting is not indicated to prevent a recurrence. Obviously, when dealing with mongols or other mental defectives, protective measures become more important and one is even less inclined to undertake keratoplasty. Many other forms of treatment have been tried: anterior chamber paracentesis, puncture of the main fluid-containing bulla, cautery to the tip of the cone, tarsorrhaphy, keratoplasty during the acute phase, pressure bandaging, and Diamox to lower the intraocular pressure. Pressure bandaging is widely held to be an important element in the treatment of acute keratoconus, but it is difficult to see what influence it can have on the healing of Descemet's membrane and the corneal endothelium. Topical steroids may lessen any tendency to corneal scarring, but against their use is the risk of accelerating the thinning process and, more seriously, of inducing a rise in intraocular pressure in susceptible subjects.

Of the five eyes dealt with in this paper, four resolved completely with a variety of treatments. The fifth eye perforated after resolution of the acute episode during a period away from medical observation. The behaviour of these eyes bears out the self-limiting nature of the condition and the need for only supportive treatment.

In the past acute keratoconus has been regarded as an extreme rarity. Now, with the increased life expectancy of mongols, ophthalmologists should be prepared to see more examples of this dramatic condition.

Summary

Three cases of acute keratoconus in mongols are described. Possible aetiological factors and management are discussed.

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Pterygium in Ceylon

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The geographical situation of Ceylon led Cameron (1965) to suggest that the pterygium rate there would range from 5·5 to over 10 per cent., but the actual incidence appears to be much less for reasons which are discussed below.

The incidence of pterygium has not been closely studied, first perhaps because it rarely causes blindness, secondly because the world's earliest eye hospitals were situated in temperate climates where the condition is rare, and thirdly because it has not attracted the interest of ophthalmic surgeons in the same way as cataract, retinal detachment, strabismus, and corneal grafting. The surgery of pterygium tends to be labelled 'minor' and to be relegated to assistants.

The chief method of assessment has been the compilation of statistics based on hospital and private practice; it is difficult to obtain figures for a whole population except in small and accessible groups.

Cameron (1965) found an incidence of 12·3, 10·9, and 14·0 per cent. in three ophthalmic practices in and around Brisbane. Alvaro found a rate of 4·9 per cent. in a hospital practice in Rio de Janeiro (Anderson, 1954). Dimitry (1937) estimated the rate in the United States of America by studying the percentage of pterygium operations. States lying close to the equator showed an average of 7 per cent., while those lying further north showed an average of 2·5 per cent. and those beyond Lat. 40° North an average of 2 per cent.

Similarly, in the Princess Alexandra Hospital in Brisbane, the rate for July to December, 1961, was 15·9 per cent. (Cameron, 1965), and Law (1959) found that in Brisbane there was a percentage of 40·5 pterygium operations in a total of 700, whereas there was not one among 36,000 patients attending the Westminster Hospital, London.

Saif, El Gammal, Barrada, and Mahfouz (1967) reported 54,187 pterygium operations out of 577,428 eye operations for the years 1953–56, 1961, and 1964 in Egypt, which gives an incidence of 9·3 per cent.

Corboy (1941) found an incidence of 17 per cent. in a population of 503 plantation workers and Crawford (1944) estimated an overall incidence of 14 per cent. in Hawaii.

Mann (1961) found 6·75 per cent. among 402 persons forming the entire population of Cocos, and 2·7 per cent. among 650 persons in the Marshall Islands.

Present investigations

This study is based on data collected in Ceylon from three sources:

(1) Hospital attendances at seven representative areas in Ceylon – The Eye Hospital, Colombo, and the departments of ophthalmology attached to six provincial hospitals (total 81,107).

(2) Attendances at a free eye clinic in the city of Colombo (total 1,202).

(3) Major eye operations carried out over a period of 18 years by the author (total 9,211).

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Results

Table I summarizes the percentage incidence of pterygium in these categories. The 81,107 patients in the hospital series were seen in the seven areas shown in the map, and the percentage in these areas ranges from 1 to 0·57 (Table II). Of the four areas with a higher percentage, two are on the coast (Colombo and Negombo-Chilaw-Puttalam), but there is a low incidence in Jaffna and Batticaloa, which are also coastal areas well known for their fishing industry. Kandy, situated in the hills, has a lower incidence, but it is not truly representative of the central highlands and, as there are no eye centres in the higher hill country, statistics there have been difficult to obtain.

Table I *Sources of data*

Source of data	*Patients seen or operated on*		
	Total No.	*Pterygium cases*	
		No.	*Per cent.*
Hospital attendances, 1965—1967	81,107	592	0·7
Attendances at a charity clinic in Colombo	1,202	10	0·8
Author's major eye operations	9,211	55	0·6

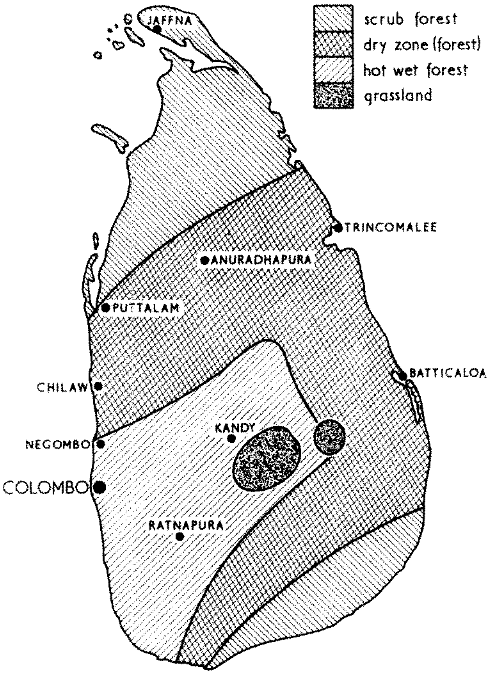

FIGURE *Map of Ceylon to show vegetation and location of ophthalmic clinics*

Sex distribution (Table III) There are more male than female patients except in Negombo-Chilaw-Puttalam, and here the women take a greater part in the fishing industry.

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Age distribution (Table IV) The incidence of pterygium increases with age and this suggests that it is more likely to affect those who have been longer exposed to the climatic or occupational conditions which favour its development.

Table II *Incidence of pterygium among hospital patients in seven principal areas*

Station	*Total cases seen*	*Total cases of pterygium*	
		No.	*Per cent.*
Colombo	10,000	73	0·75
Ratnapura	18,828	155	0·8
Batticaloa	24,000	146	0·6
Jaffna	9.000	53	0·57
Negombo-Chilaw-Puttalam	9,000	98	1·0
Kandy	6,463	44	0·6
Anuradhapura-Trincomalee	2,716	23	0·8
Total	81,107	592	0·7

Table III *Incidence of pterygium, by sex*

Station	*Total Cases*	*Males*		*Females*	
		No.	*Per cent.*	*No.*	*Per cent.*
Colombo	73	55	75	18	25
Ratnapura	155	118	76	37	24
Batticaloa	146	94	64	52	36
Jaffna	53	34	64	19	36
Negombo-Chilaw-Puttalam	98	50	51	48	49
Kandy	44	30	68	14	32
Anuradhapura-Trincomalee	23	17	74	6	26
Total	592	398	66·5	194	33·5

Table IV *Incidence of pterygium, by age*

Age (yrs)	*Cases of pterygium*	
	No.	*Per cent.*
0–9	2	0·9
10–19	18	3
20–29	93	15
30–39	152	25·6
40–49	145	25
50–59	115	19·6
60–69	58	10
70 and over	9	1·5
Total	592	100·0

Climate of Ceylon

The island lies in the Indian Ocean between Lat. 6° and 10° N. It is 250 miles long and 135 miles wide, and the central highlands rise to a height of nearly 9,000 ft. The two monsoons, the South-west from May to July and the North-east from October to December, bring a fairly heavy rainfall. The luxuriant vegetation includes wet and dry zone forests, scrub forest, and grasslands (see Map). The surrounding sea with numerous lagoons and rivers maintains an equable temperature, averaging 80°F. in the lowlands and 60°F. in the hills. The amount of cloud cover, an aspect of climatology of special significance in the aetiology of pterygium, is shown in Table V (overleaf).

The insolation, rainfall, humidity, and wind speeds are given in Tables VI and VII (overleaf).

Table V *Cloud cover over areas studied**

Station	*Month* *Feb.*	 *Jun.*	 *Nov.*
Colombo	4·0	6·6	5·5
Ratnapura	4·9	6·9	5·9
Batticaloa	4·7	4·7	5·2
Puttalam	3·5	6·0	5·2
Jaffna	3·4	5·0	5·4
Kandy	3·9	6·6	5·6
Anuradhapura	4·1	5·9	5·6

*30-year average, 1931 to 1960; Maximum = 8
(Mean of 08·30 and 17·30 hrs)

Table VI *Insolation (Colombo)*

Phenomenon	*Quantities*
Hours of sunshine	12
Elevation of sun	90° at noon
Total radiation, Sun/Sky (monthly totals)	15,750 Cals/cm.^{2} March 9,843 Cals/cm.^{2} December
Ultra-violet radiation 1,000–3,000 Å (calculated)	0·02 microwatts/cm.^{2}/min. at noon

Table VII *Rainfall, humidity, and wind speed* (30-year average, 1931–60)

Station	*Rainfall (in.)*	*Per cent. humidity* *Day*	 *Night*	*Wind speed* *Miles/hr*
Colombo	94·3	76	89	5
Ratnapura	153·1	76	93	–
Batticaloa	66·9	74	87	7
Jaffna	52·3	76	86	10
Negombo	77·2	72	90	–
Puttalam	43·6	74	88	8
Anuradhapura	56·8	70	92	–
Trincomalee	67·9	70	83	9

Comment

In Ceylon, where the demand for ocular surgery is mainly for blinding or painful eye conditions, cosmetic surgery is not much sought after and few patients would seek removal of pterygia. The statistics provided by general ophthalmic practice are therefore more reliable. It is accepted the pterygium occurs in an equatorial belt delimited by Lat. 40°N and S (Cameron, 1965; Elliot, 1966), and Cameron's study of the relationship between ultra-violet light in different parts of the world and the incidence of pterygium was the first indication of the causation of this condition.

No absolute values of the incident ultra-violet radiation are available for Ceylon. The calculated value in Table VI does not entirely cover the wavelengths that reach the surface of the earth and one has, therefore, to rely on the premise that ultra-violet radiation over Ceylon must equal that over other parts of the world at similar latitudes.

According to Cameron's calculations the expected pterygium rate in Ceylon should be more than 10 per cent. as in other lands in the same latitude, and his map depicting the world distribution of pterygium computes a rate of 5 to 9 per cent., but the figures presented above show a much lower incidence of only 0·57 to 0·8 per cent.

The chief reason for this difference must be the humidity and abundant rainfall, leading to thick vegetation and absence of solar glare. Elliott (1966) has, in fact, stated that the incidence of pterygium in equatorial regions may still be low provided a high humidity prevails and direct or reflected solar radiation is rendered less harsh by dense vegetation.

Summary

No information on the incidence of pterygium in Ceylon has so far been available, except the pterygium maps compiled by Cameron (1956), according to which the rate should be between 5 and 10 per cent. Data from hospital attendances in seven different areas, attendances at a charity eye clinic in Colombo, and numbers of pterygium operations performed by the author in the past 18 years give rates of 0·7, 0·8, and 0·6 per cent. respectively.

My thanks are due to the following ophthalmologists for placing at my disposal material collected in their areas: Dr. Arunachalam (*Batticaloa*), Dr. Gunasekera (*Negombo-Chilaw-Puttalam*), Dr. Monica Jayasuriya (*Ratnapura*), Dr. Sivarajah (*Jaffna*), Dr. Sivalingham (*Kandy*), Dr. Wirasinha (*Kandy*), and Dr. Abeysuriya (*Anuradhapura-Trincomalee*), and also to Padma Wickremasinghe (*Registrar, Eye Hospital, Colombo*), Dr. L. A. D. I. Ekanayake, Director, Department of Meterology, Ceylon, for his valuable assistance with statistics relating to the climatology of Ceylon, and Dr. R. Sivaramalingham of the Ceylon Institute of Scientific and Industrial Research, with calculations of ultra-violet radiation.

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Retinal hazards during laser irradiation of the iris

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Transpupillary pulsed laser radiation has been extensively studied to determine both the level at which it becomes a hazard to the retina (Ham, Williams, Mueller, Guerry, Clarke, and Geeraets, 1966), and its effects on that tissue when such levels are exceeded (Marshall and Mellerio, 1967a,b, 1968). In spite of the development of various codes of practice to protect users, several accidents have been reported (Rathkey, 1965; Zweng, 1967; Curtin and Boyden, 1968). More recently an attempt has been made to evaluate trans-scleral hazards (Smith and Stein, 1968, 1969), and safe levels have now been defined for both ruby and neodymium laser beams entering the eye through this tissue.

No investigative work has so far been carried out on the possible transmission of laser beams impinging on the iris. Such an event might take place under two circumstances; first, with the eye open the iris may contribute up to half the exposed area of the globe and thus form a significant target for laser beams accidentally discharged towards the eye. Secondly, it may be necessary to fire laser beams directly at the iris for clinical reasons; peripheral iridotomy by laser has been discussed in the literature (Flocks and Zweng, 1964; Hallman, Perkins, Watts, and Wheeler, 1968), and retinal hazards commented upon (Snyder, 1967), but no practical measurements of such hazards have been made.

The aim of this work is to study the spectral characteristics of the iris to non-coherent light and (to a limited extent) laser light, and predict the possible hazards of trans-iridial laser radiation.

Experimental methods

A. NON-COHERENT LIGHT

The first problem in attempts to measure the spectral characteristics of the iris was the mounting of the specimens. The tissue stretches easily and thus required not only a firm base but careful control of its thickness. The thickness of the iris *in vivo* varies with the size of the pupil, and the following method was designed to give a preparation which could be handled easily and ensure that each iris was examined under similar conditions. Although the absolute values obtained with this method may not correspond to the iris in its normal state, comparative values for transmission and reflectance at different wavelengths and with different coloured irides should still be valid.

The iris samples were prepared from freshly enucleated rabbit eyes; the dissection procedure was simple but, in view of the relatively fragile nature of the unfixed iris, extreme care was required. The posterior segment of the globe was cut away and the anterior segment was held face downwards in a dish while capsule forceps were slipped beneath the lens to lift it away from the underlying pigment epithelial layers of the iris. The iris was removed by seizing its periphery with a pair of toothed forceps and gently tugging. Provided that reasonable care was taken, the whole tissue could then be removed intact. A single radial cut from pupil to periphery enabled the iris to be laid flat on a microscope slide in a pool of saline and smoothed out. A second slide was then placed over the preparation and the tissue compressed until it had only the thickness of the single cover

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slip placed between the slides at either end. Excess saline was wiped away with filter paper and the ends of the slides were bound together with adhesive tape. In this way consistent preparations could be made.

Each preparation was mounted over the window of the cell-holder of a Unicam S.P. 500 spectrophotometer, and transmission values were measured in steps of 500 Å. Before each measurement, the photocell dark-current was zeroed and a control blank of two plane glass microscope slides was placed in the beam path; the aperture of the photocell was opened and the machine re-zeroed, thus correcting for absorption due to the glass. The same tungsten light source was used for the whole wavelength range, but two photo cells were necessary: a red-sensitive one between 11,000 and 6,250 Å and a blue-sensitive one over the rest of the range.

In addition to the preparation of iris, a model experiment was carried out on a melanin suspension. Two slides were prepared, one coated with 5 per cent. gelatin and the other with a suspension of 15 mg./ml. powdered melanin in 5 per cent. gelatin. These slides were scanned over the same wavelength range in the spectrophotometer, the gelatin-only slide serving as a control.

For determination of the reflectance of the irides, the same method of preparation was adopted and the specimens scanned in a Beckman recording spectroreflectometer. This intsrument works by comparing the reflectivity of the test surface with that of a standard reflector, the differences between the two being recorded by the movement of a pen over a chart calibrated according to wavelength. Eight albino, eight brown, and three blue irides, each with the minimum area of 10 × 6 mm. required by the apparatus, were prepared and mounted as described. Each sample was placed behind one window of the measuring sphere of the apparatus and a standard white tile behind the other, the pair then being scanned over the wavelength range 5,000 Å to 11,000 Å. The reflectance values at various wavelengths were read at 500 Å intervals from each of the recordings, and the mean at each wavelength was calculated. At this stage all readings represented percentage reflections relative to the white standard tile which was itself not 100 per cent. reflecting; to arrive at the final percentages, a correction had to be made to each mean reading from a graph of the known absolute reflection characteristics of the tile as supplied by its manufacturers. The final percentage reflections were plotted as a function of the incident wavelength.

B. LASER LIGHT

The experiments with laser light were restricted to the passive ruby laser and fell into two categories:

(1) The first series of experiments was designed to measure the absolute transmission of a laser beam through the iris by direct calorimetric recording. The iris was dissected out of each specimen as previously described and placed, pigment epithelium downwards, on a cover slip by which it was transferred to a specially constructed glass cell. A blunt seeker was used to manoeuvre the iris from the cover slip onto the inner wall of the rear face of the cell where surface tension sufficed to hold it in place. The cell was then filled with a silicone fluid (Midland Silicones, 200/1 cSt) and the rear surface was optically masked with black paper, leaving only a hole the size and shape of the tissue. The cell was mounted vertically in front of, and closely opposed to, the measuring cone of a calorimeter (Laser Associates) so that all light passing through the iris would enter the measuring device no matter how much it deviated. The laser, mounted on a Gambs photo slit lamp (Hallman and others, 1968) was aligned in front of the cell so that its beam was focused at the plane of the iris. The cell was movable by means of a vertical and horizontal racking device, so that any part of the iris could be lasered and its transmission recorded. Between eight and fifteen lesions were made on each of the irides used, and the mean transmission was calculated from the recordings; at the end of the experiment the incident energy was measured by firing the laser six times into the calorimeter through cell and fluid alone, the iris having been removed. A beam-splitting device enabling individual shots to be monitored would have been preferable but was not available, and so the experiments were based on the assumption of stability in the laser output. To minimize variation in output, the firings were separated by a fixed time interval of 5 min. The percentage transmission of the irides was calculated from the mean transmission values and mean output of the laser.

A slight variation of this method was used in the case of an albino iris; instead of using the same incident energy at each firing, the transmission was measured at the full range of switched energy steps available from the laser. Incident and transmitted energies at each level were plotted against one another, the result being a straight-line graph, the slope of which gave another indication of percentage transmission.

(2) The geometry of the transmitted beam was investigated to discover whether it remained a discrete, though less energetic, beam or was diffused by its passage through the tissue. The principle of the experiment was similar to the previous one except that instead of the calorimeter, an unexposed Ilford R.10 photographic plate was placed directly behind the cell. In one experiment the developed plate was replaced behind the cell in an identical position to that which it had occupied before exposure, the iris was removed, and the laser fired again. The plate, blackened by development, presented an absorbing filter to the beam which caused a burn on the gelatin film indicating where the original beam would have impinged in the absence of the iris. Other exposed and developed plates were then searched in corresponding areas for evidence of an undiffused beam. To relate the experiment more closely to the condition *in vivo*, it was repeated with a whole anterior segment—iris, cornea, and lens—held together by a 3 mm. rim of sclera. The preparation was suspended in a similar but deeper glass cell by cotton sutures through the scleral rim, and subjected to the same treatment.

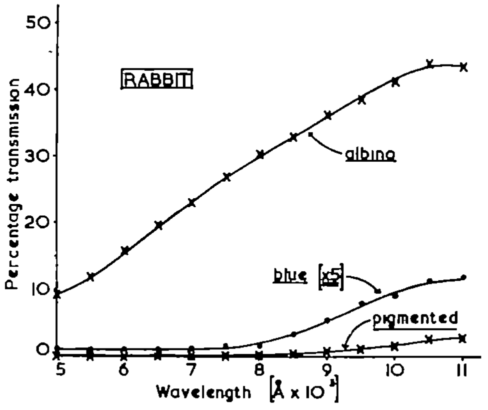

FIG. 1 *Spectrophotometer transmission readings of rabbit irides compressed to a uniform thickness between two microscope slides. The values for the blue iris are shown multiplied by 5 to separate them from those of the brown iris*

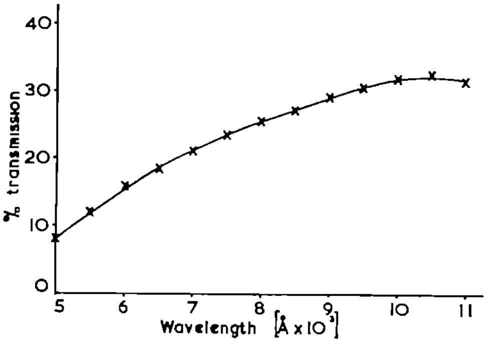

FIG. 2 *Transmission of a suspension of melanin granules in gelatin*

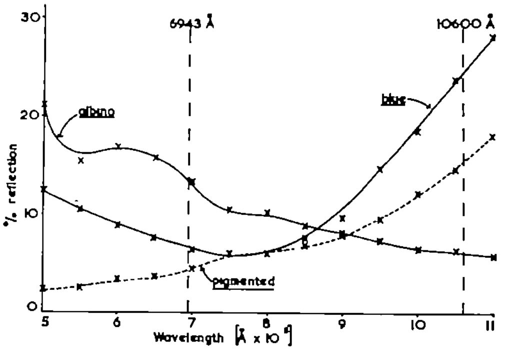

FIG. 3 *Reflectivity of blue, brown (pigmented), and albino rabbit irides as measured in a spectroreflectometer*

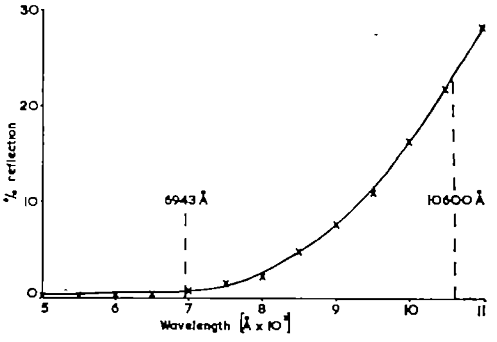

FIG. 4 *Reflectivity of the pigment epithelium of a pigmented rabbit iris*

Results

The measurements of non-coherent light transmission and reflection are presented graphically (Figs 1 to 4), and the transmission of the laser numerically (Table). The pigmented rabbit iris irradiated with 200 mJ of ruby laser light yielded a transmission value so far below 1 per cent. that it was not considered either valid or useful to measure it precisely. The value of 30 per cent. for the albino iris is in good agreement with the value of 29 per cent. calculated from the graph of transmission at various incident energies (Fig. 5).

Table *Mean transmission in a series of experiments with irides of different colours*

Iris type	*No. of recordings*	*Mean transmission (per cent.)*	*Standard deviation*
Albino	75 lesions in five eyes	30·1	1·8
Blue	43 lesions in four eyes	4·2	1·7
Brown	60 lesions in five eyes	< 1	—

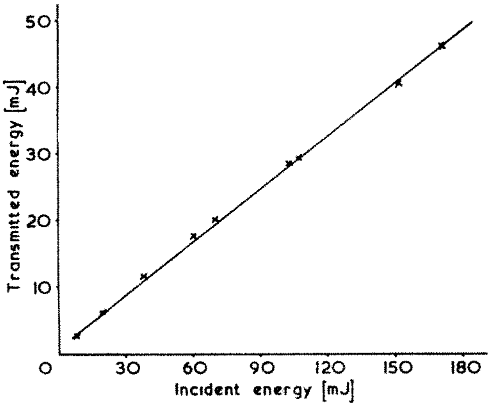

FIG. 5 *Transmission at various energies of an albino rabbit iris*

The photographic recordings revealed no indication of a discrete spot on the plates behind either the pigmented or albino rabbit irides (Figs 6*a* and *b*, overleaf). Although the plates were located directly behind the cell, and therefore only a few millimetres from the back of the lesion, albino irides caused the emulsion to be fogged over a roughly circular area 3 cm. in diameter. The results, both from isolated irides and whole anterior segments, were similar (Figs 6*c* and *d*, overleaf).

Discussion

Several papers have been published concerning light transmission through the ocular media (Wiesinger, Schmidt, Williams, Tiller, Ruffin, Guerry, and Ham, 1956), the retina and choroid (Geeraets, Everett, and Guerry, 1962), and even the sclera (Smith and Stein, 1968). The iris, however, has escaped attention. As mentioned earlier, its contractile nature leads to variations in thickness which would possibly alter its transmission characteristics. The figures quoted here for laser transmissions must be regarded only as indications of the levels to be expected.

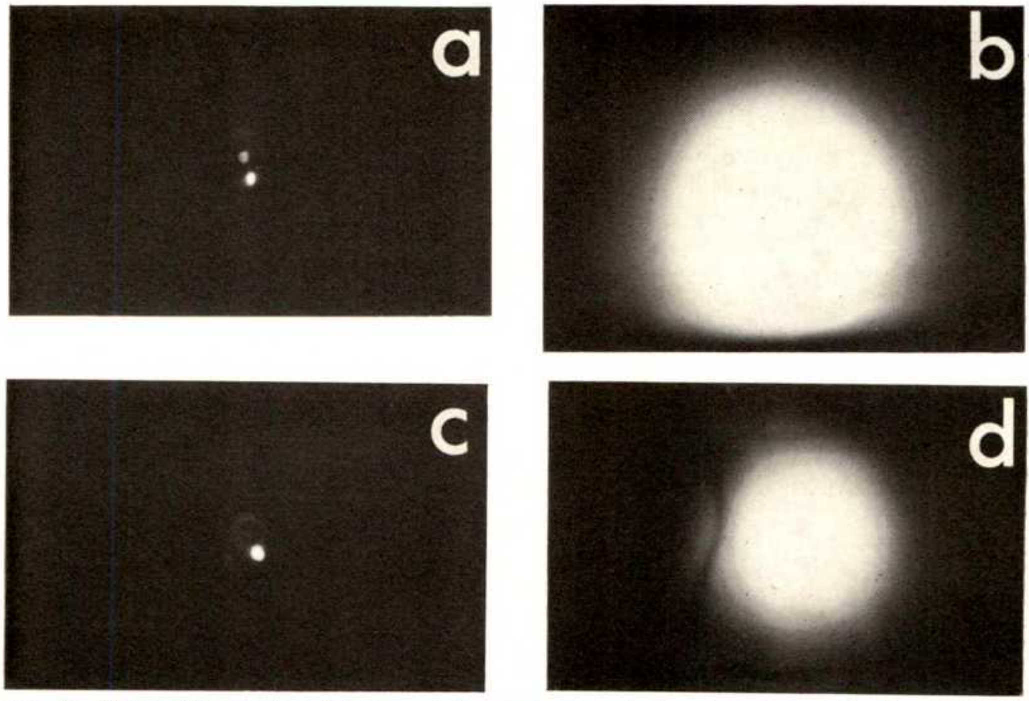

FIG. 6 *Photographic recording of the transmission of a passive ruby laser beam through the albino rabbit iris*

(*a*) The unimpeded beam before interposition of the iris into the cell between laser and photographic plate. The beam is the lower and more intense of the two white spots; the upper is a reflection artefact from the walls of the glass cell

(*b*) The beam after trans-iridial passage

(*c*) As (*a*), but using a deeper cell

(*d*) The beam after passage across a whole anterior segment instead of an iris alone

A few workers have examined uveal pigment either isolated (Pakkenberg, 1966) or in sections of the iris (Jensen, 1969), but no studies appear to have been performed on the properties of the whole tissue. Figs 1 and 2 indicate that increase in transmission with wavelength is a general property of both the tissue and its pigment over the range examined; this is comparable with the findings of Pakkenberg (1966) on individual pigment cells over the same region of the visible spectrum. It might be argued that this apparent increase in transmission is merely a by-product of a decreased reflection (which would make more incident energy available) at longer wavelengths. Fig. 3 reveals that this is not the case, at least for the blue and brown irides which actually reflect more at the longer wavelengths. The albino iris does not show this tendency, which partly accounts for the steep rise in transmission in Fig. 1 compared with the curves for the pigmented irides. The general slope of the curves, including the suggestion of a peak around 10–11,000 Å, resembles Smith and Stein's results for the combined sclera, choroid, and retina.

The reflection curves of the iris are slightly more complicated than its transmission curves, and pigment-free tissue exhibited properties different from those of its isolated pigment. Inspection of Fig. 4 shows that reflection from the pigment alone increases at longer wavelengths while that from albino tissue (Fig. 3) decreases. The U-shaped curve for the blue iris (Fig. 3) may thus be seen as a combination of high reflection from the tissue stroma at short wavelengths and from the pigment epithelium at longer wave-

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lengths. No explanation can be advanced for the slight hump in the albino curve at 6,000 Å, but a similar peak was found by Smith and Stein (1968) in their studies on reflectance of the rabbit sclera, another pigment-free tissue.

The curves in Figs 1 and 3 suggest that the iris will react differently to the two most commonly used pulsed lasers (ruby at 6,943 Å and neodymium at 10,600 Å). The pigmented rabbit iris reflects a greater proportion of neodymium than of ruby laser light; furthermore, of the reduced amount of neodymium laser energy actually penetrating the surface of the iris, more is transmitted through it. The total absorption is thus lower and the neodymium laser represents a smaller hazard to the iris tissue than the ruby laser. This slight disparity of incident energy (further enhanced by the extra absorption of near infra-red light in the ocular media) is apparent in the lesions caused by a neodymium laser *in vivo* (unpublished data). As regards damage to the fundus, the neodymium laser with its higher transmission represents the greater danger, and in clinical work such as iridotomy where the object would be to confine damage to the iris, it is quite clearly contraindicated by comparison with the ruby laser. Optimum clinical results should (by reference to Figs 1 and 3) be achieved using a pulsed laser with a shorter wavelength than the ruby laser. While having a high transmission in the ocular media, reflection from the surface of the iris would be low and absorption within its depth would be high. For example, the frequency-doubled neodymium laser operating at 5,300 Å (yellow-green) should give better results, but the difference might well prove to be marginal.

Densitometric studies of unstained sections of the brown rabbit iris (Hallman and others, 1968) indicate that the bulk of the tissue pigment is in the pigment epithelium, the remainder being concentrated in the anterior layers of the stroma. The blue iris is entirely devoid of stromal pigment, but has a normal epithelium. The similarity of the laser transmission results for the blue and brown rabbit irides is thus not surprising; compared with the pigment in the epithelium, the stromal pigment of the rabbit represents a minimal barrier.

Accepting that a little light does pass the pigment epithelium, the photographic recordings of the transmitted beam would seem to indicate that it is very unlikely to cause retinal damage. The iris acts not only as an optical filter (Fig. 5) but the photographs (Fig. 6) indicate that it also acts as a very efficient diffuser of the laser beam.

In an attempt to relate this work directly to the human iris, several cadaver eyes were obtained from the Moorfields Hospital Eye Bank, and subjected to laser transmission studies identical to those performed on the rabbit. However, despite refrigeration for the 2 to 3 day period between enucleation and use, the pigment epithelium tends to be dislodged more easily after storage (Kaczurowski, 1965), and it is more susceptible to damage during dissection, an important point if it is borne in mind that this single cell layer plays a major role in light absorption. The transmission values of the human iris showed considerably more scatter than those of the rabbit, and the mean values were 5·5 per cent. (S.D. 2·8 per cent.) for a brown iris (30 lesions on 3 eyes), and 14 per cent. (S.D. 6·3 per cent.) for a blue iris (29 lesions on 3 eyes). It is difficult to calculate the energy density incident upon the retina due to transiridial passage, but it must be well below the damage threshold. This is generally considered to be 0·7 J/cm.^{2} (Ham and others, 1966) so that, even if 20 per cent. of a 200 mJ clinical exposure was transmitted, it would represent only 0·04 J over the whole of the fundus. The only danger would arise if a laser was discharged at an area of the iris which had already undergone atrophy (Snyder, 1967); retinal damage might then be sustained. However, prior transillumination of the iris should be sufficient to reveal any such areas.

Assuming that the light transmitted through the iris is dispersed evenly over the posterior half of the globe, calculation shows that the incident beam may have an energy density of several hundred J/cm.^{2} before the retinal threshold is reached. However, there is no guarantee that the diffusing properties of the iris will remain the same at high energies; that proportion of the laser beam absorbed as a result of the optical filtering by tissue causes it to undergo partial destruction. In a beam approximately 1·2 mm. diameter, destruction starts at an energy of about 15 m J, *i.e.* an energy density of 1·1 J/cm.^{2}, and at 16 J/cm.^{2}, the pigment epithelium is completely shattered. It may then be assumed that, above 16 J/cm.^{2}, the percentage of laser light transmitted through a brown iris will increase; it is also possible that the damage to the iris will not only permit the passage of more light, but that this light may be in a more geometrically concentrated beam and will therefore constitute a greater hazard.

Nothing has yet been said of the structure closest to the iris, the lens. Since its epithelium is closely apposed to the pigment epithelium of the iris, cataractogenetic heating of the lens surface might be suspected. Indeed, this is the subject of a recent paper by Leibowitz and Luzzio (1970), who produced numerous cataracts with a ruby laser at an energy density of 29·5 J/cm.^{2}. However, at the level of about 16 J/cm.^{2} used in this work, no sign of cataract was seen in rabbits either killed immediately or kept for periods of up to 18 months. On the basis of Leibowitz and Luzzio's data, a few cataracts might have been expected in this work. The explanation probably lies in the differing experimental conditions; Leibowitz and Luzzio lasered the whole anterior segment of the eye while lesions in the present work were localized and only a little over 1 mm. in diameter. Thus, while the energy densities were not so far removed, the absolute energies used differed by perhaps two orders of magnitude. In a small closed-box system like the eye, this would tend to render the experiments incomparable. However, while lens damage constitutes a potential hazard, it is not strictly within the province of this paper and will be discussed no further.

Conclusions

(1) The neodymium laser applied to the iris constitutes a greater retinal hazard than the ruby laser.

(2) The stored human irides used in this work exhibited a higher transmission than did those of the rabbit eyes.

(3) The iris acts as an optical diffuser as well as an attenuator.

(4) Transmitted ruby laser light from a clinical exposure to the iris of up to 16 J/cm.^{2} is unlikely to induce retinal damage.

(5) Above 16 J/cm.^{2}, the integrity of the pigment epithelium is lost and the diffusing properties of the iris may well decline, thus disproportionately increasing the dangers from transmitted energy.

Summary

Rabbit irides (albino, blue, and brown) were subjected to spectrophotometry and spectroreflectometry to assess their transmission and reflection properties to light between 5,000 and 11,000 Å. The geometry and energy of a ruby laser beam transmitted through the iris were assessed by placing a photographic plate and calorimeter respectively behind a test specimen during irradiation. Several irides were similarly investigated.

From this data, the possible hazards to the retina from clinical or accidental exposure of the iris were evaluated.

I should like to thank Prof. E. S. Perkins for advice and encouragement and Mr. M. S. Bass for his skilled technical assistance.

Dr. K. Rassum of Imperial College, London, kindly provided facilities for the reflection measurements. This work was supported by a grant from the Ministry of Defence.

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Foetal cleft anomalies of the anterior chamber

RONALD F. LOWE

From the Glaucoma Unit, The Royal Victorian Eye and Ear Hospital, Melbourne, and the Ophthalmic Research Institute of Australia

Sampaolesi (1968) described, and carefully illustrated, malformations in the region of the optic cup showing as depression of the surface of the iris, recession of the angle, and increase of the anterior chamber depth in that sector. Finding these signs in adults with chronic glaucoma, he postulated a more widespread disturbance of the angle structure and considered that the glaucoma was a form of secondary glaucoma having a congenital origin but with late onset.

For several years independently on the other side of the world, I have been observing these malformations during the examination of patients with angle-closure glaucoma, and I have come to different conclusions.

Fuchs (1885) described a frequent hypoplasia of the mesenchymal layer of the iris in the region of the foetal ocular cleft. Further descriptions were added by Arnold (1911), Streiff (1915), and Mann (1937). The observations were confirmed by Vogt (1941) and Berliner (1949), who gave illustrations in their text books. These authors describe segmental iris thinning inferiorly, sometimes with extensions centrally that caused a small notch in the inferior margin of the pupil. Their publications preceded widespread gonioscopy, so that descriptions of the angle are lacking except that Streiff (1916) illustrated, in section, a steeper depth of the angle in this place.

Descriptions

The anomalies show as consequences of minor irregularities in closure of the foetal cleft. Characteristically the situation is inferonasal, but may be directly inferior or occasionally slightly inferotemporal in positions found for congenital colobomata of the iris.

Minimum anomalies show as dimples in the periphery of the iris, usually suggesting slight fibrosis at the site of closure of this part of the cleft. These dimples are readily seen when the remainder of the iris is convex as a result of relative pupil block in primary angle-closure glaucoma (Fig. 1).

More extensive irregularities show as larger depressions of the peripheral iris or extensions centrally that cause a slight thinning of the iris stroma even as far as the inferior margin of the pupil to produce a slight notching there (Fig. 2). The depression of the peripheral iris may also become more obvious with pupil dilatation after iridectomy, when folded iris crowds the angle elsewhere (Fig. 3). Peripheral foetal cleft anomalies may be seen open to the depths of angles that are otherwise completely occluded.

Significance

The generally agreed frequency of these anomalies indicates that they have no adverse effect on ocular function. My observations in their relationship to angle-closure glaucoma

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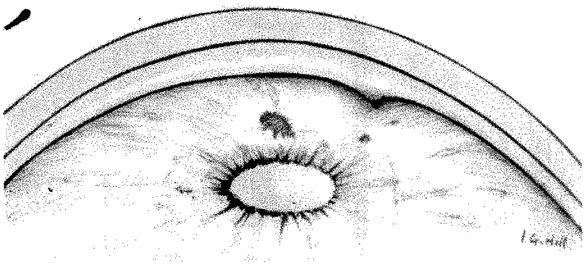

FIG. 1 *Peripheral iris dimple with convex iris and narrow angle.*

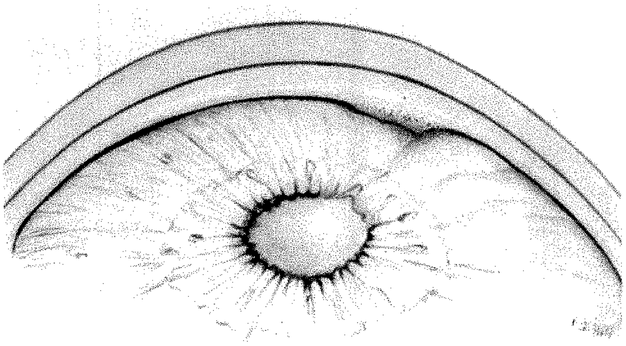

FIG. 2 *Peripheral iris indentation with radial iris anomaly and notched pupil.*

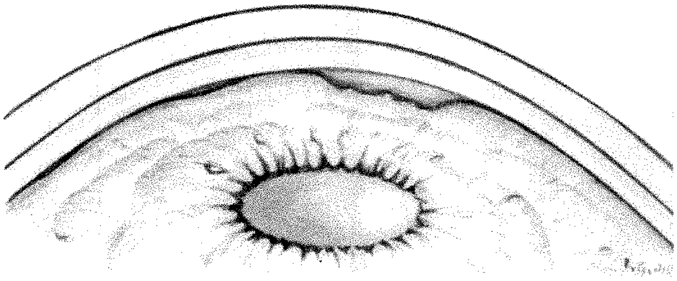

FIG. 3 *With pupil dilatation, the peripheral iris indentation remains wide while the angle is crowded elsewhere.*

show no increased tendency for chronic glaucoma to follow peripheral iridectomy for the control of angle closure.

For glaucoma, the significance of these foetal cleft anomalies appears to be related to theories concerning the mechanism of angle closure and the possibility of reducing its risk.

The suction theory of angle closure

The importance of relative pupil block as an essential feature of primary angle-closure glaucoma now appears beyond dispute, but the mechanism of actual angle closure still has some controversial aspects.

Czermak (1897) postulated that the peripheral iris was sucked against the trabeculae. This concept was supported and developed by Posner (1953), who later stated (Posner 1955) that the iris suction hypothesis presupposed not only the presence of a narrow angle but also a continuous and unbroken surface of the iris where it comes into contact with the cornea to make a watertight seal. If the seal were broken in any place, the suction would be lost and the angle would open. Further, in the fellow eyes of some cases of primary angle-closure glaucoma, he found crypts, in the peripheral iris stroma which he believed prevented angle closure by allowing communication of aqueous to the annulus between the convex iris and trabeculae so that suction onto the iris could not occur (Posner, 1955).

The congenital cleft anomalies refute the circular suction theory and the importance of peripheral iris crypts.

The suction theory refuted

In some cases of acute angle-closure glaucoma, a deep dimple of the peripheral iris associated with a corresponding opening into the angle can be seen while the remainder of the angle is closed and the ocular tension is high. If treated sufficiently early these angles will open; but, if the patients have delayed attending until firm peripheral anterior synechiae have formed, the angles will remain closed despite surgery; yet the peripheral clefts may still be seen open to the depths of the angles.

In acute angle-closure glaucoma, sometimes following preliminary intensive treatment which opens the angle, and especially after the convexity of the iris has been abolished by surgery, a large section of the inferior angle may become suprisingly wide. Gonioscopically, the full depths of the inferior angle are then easily seen despite the angle remaining narrow above. Such appearances cause surprise that angle closure has occurred, but these are typical shallow anterior chamber eyes with enough relative pupil block to cause angle closure by iris convexity from posterior aqueous pressure. When the posterior aqueous pressure is relieved, the thinning of the iris and the widening of the angle from the cleft anomaly become obvious.

More rarely, a large inferior depression of the peripheral iris may be unilateral and seen in a fellow eye accompanying one with a typical convex iris and acute angle-closure glaucoma. In these uncommon cases, usually in elderly people, one anxiously debates the recommendation for performing routine peripheral iridectomy even though the anterior chamber depth be within the known range of risk.

Summary

Congenital depressions of the peripheral iris associated with closure of the foetal cleft are relatively common. Relative pupil block angle-closure glaucoma can occur in their presence. They refute the suction theory for angle-closure glaucoma and the proposition that peripheral iris crypts prevent angle-closure glaucoma. Foetal cleft anomalies in eyes subject to angle-closure glaucoma were found to have no significance for causing chronic glaucoma.

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Book reviews

Syphilis and the Eye. Edited by B. SCHWARTZ. 1970. Pp. 299, 19 figs, bibl. Livingstone, Edinburgh. (£9)

This book is essentially a hard-cover reprint of the third issue of Volume 14 of the *Survey of Ophthalmology*, and has a mainly historical approach. There are short articles on the life of Douglas Argyll Robertson and his pupil, and of Josef Igersheimer (who must have been a charming person), and a review of his book on syphilis and the eye. J. Lawton Smith again reviews the current status of ocular syphilis and Golden and Thompson admit the problem of evaluating the spiral forms found in the aqueous. There follows a historical survey of the treatment of syphilis, but one wonders how the author avoided the cautionary tale: "One night with Venus and the rest of your life with Mercury". Finally, Loewenfeld reviews almost everyone's opinion about every aspect of Argyll Robertson's pupil, with league tables showing how the authors fared.

So far, apart from the glossy format, this is still part of Volume 14. The extra delight is a 2,433 item bibliography relating to the Argyll Robertson pupil. The results cannot be commended. We are presented with a reprint of a reprint of Argyll Robertson's paper which is also included in the bibliography. One must be grateful that the other 2,432 papers were not reprinted. Surely, if this issue of the *Survey of Ophthalmology* were so out-standing a re-issue could be obtained, with the offer of a photostat of the references if needed. Your reviewer found all the articles readable, interesting, and informative. On the other hand, the policy of foisting an expensive book (£9) on to libraries and even subscribers to the present journal is to be deprecated. For once a strong protest must be made against editorial policy, and this can only be effective by not buying the book.

Textbook of the Fundus of the Eye. By A. J. BALLANTYNE and I. C. MICHAELSON. 2nd ed., 1970. Pp. 736, 821 figs, bibl. Livingstone, Edinburgh. (£15)

This is an excellent, well-organized, and well-produced book dealing with the pathological processes which may affect the vitreous, retina, Bruch's membrane, choroid, and optic nerve. Methods of examination, which are carefully described, include fluorescein angiography and ultrasonics. There are numerous reproductions of histological preparations and of the fundus.

It is a pity that more use is not made of fundus photographs, instead of the usual drawings, particularly of the optic disc. In a few cases the colour reproduction is poor. Surgical workers would perhaps prefer more detailed description of indirect ophthalmoscopy and scleral indentation.

These, however, are small criticisms which do not detract from a masterpiece which should be available to all ophthalmic surgeons, physicians, and neurologists.

Clinical Ophthalmology. Vol. 2 (Ophtalmologie clinique) Edited by G. BONAMOUR. 1970. Pp. 615, 174 figs. 6 col. pl. Doin, Paris (160 N.F.)

This is the second half of a general textbook of ophthalmology written by members of the Medical School of Lyons under the direction of Georges Bonamour. It deals with the uveal tract, vitreous, ocular motility, optic nerve, glaucoma, neuro-ophthalmology, ocular trauma, the eye and systemic disorders, poisoning, genetics, and medical treatment in ocular pathology. Like the first volume it is well written and abundantly illustrated and can be recommended to French-speaking junior ophthalmic specialists.

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Notes

North of England Ophthalmological Society

P. J. Hay Prize, 1971

The P. J. Hay prize will be awarded for a paper on a subject in ophthalmology. The successful candidate will receive a sum of money and an engraved plaque. Three copies of the paper should be submitted to the Honorary Secretary, Mr. R. Ivor T. Lloyd, 2, Walmer Villas, Bradford, BD8 7ET, Yorkshire. Closing date June 30, 1971.

Ophthalmological Society of South Africa

Congress, March, 1971

The Ophthalmological Society of South Africa will hold a Congress in Hermanus, Cape, from March 11 to 14, 1971. There will be Symposia on the cornea, glaucoma, and the posterior segment, and also free papers. Further information may be obtained from the Congress Secretary:

Dr. A. C. Neethling, 506 Medipark, Foreshore, Cape Town, South Africa.

Wills Eye Hospital and Research Institute, Philadelphia

Course on Glaucoma, April 7–9, 1971

The Glaucoma Service of the Wills Eye Hospital, affiliated with Temple University Health Sciences Center, is offering a 3-day course (limited to thirty members) on "The Management of Patients with Glaucoma", on April 7 to 9, 1971. The tuition fee of $150 covers tuition, luncheon, and a concert by the Philadelphia Orchestra. Inquiries should be addressed to G. L. Spaeth, M.D., Director, Glaucoma Service, Wills Eye Hospital, Philadelphia, Pa. 19130, U.S.A.

Irish Ophthalmological Society

Montgomery Lecture, 1971

The Irish Ophthalmological Society will meet in Dublin on April 29 and 30, 1971. The Montgomery Lecture will be delivered at the Royal College of Surgeons in Ireland on the afternoon of April 29, by Mr. L. P. Jameson-Evans, F.R.C.S. (Birmingham).

V Pan-hellenic Ophthalmological Congress

Rhodes, May 28–30, 1971

The V Pan-hellenic Ophthalmological Congress will be held in Rhodes from May 28–30, 1971. The main subject for discussion is "Modern aspects of the vascular diseases of the retina".

For further information write to the Secretariat of the V Pan-hellenic Ophthalmological Congress, c/o Hellenic Ophthalmological Society, Elefteriou Venizelou 26A, Athens-135, Greece.

William Mackenzie Medal, 1971

Prof. Stephen M. Drance, of the University of British Columbia, has been awarded the William MacKenzie Medal for 1971 for his researches on the optic nerve.

Corrigendum

The claim of the authors of the article on "Rhinosporidium granuloma of the conjunctiva with scleral ectasia", which appeared last year in this journal (*Brit. J. Ophthal.*, 1970, **54**, 565), that theirs is the second case in the world literature is not correct. We have a letter from Dr. P. N. Srinivasa Rao pointing out that he described such a case in the *J. All-India ophthal. Soc.* (1969), **17**, 59.

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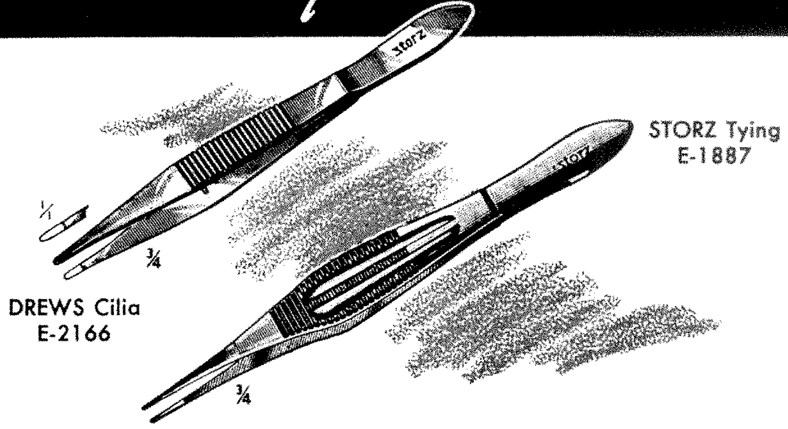

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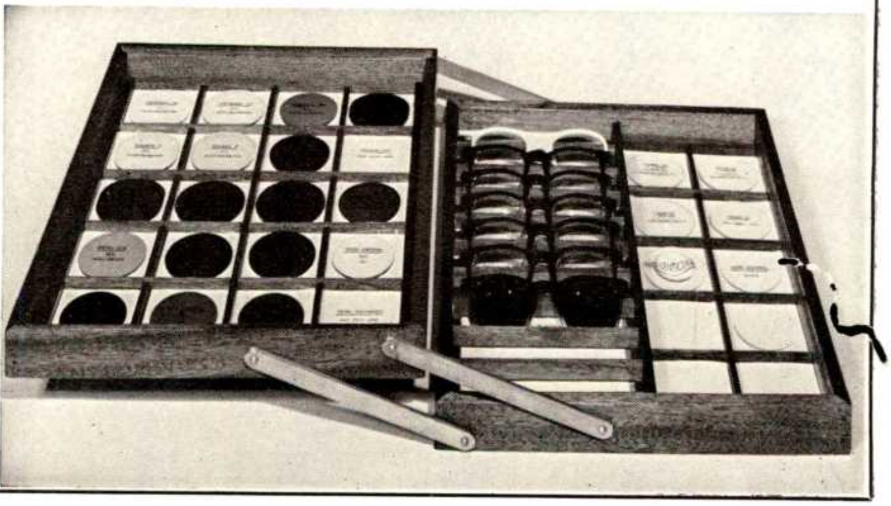

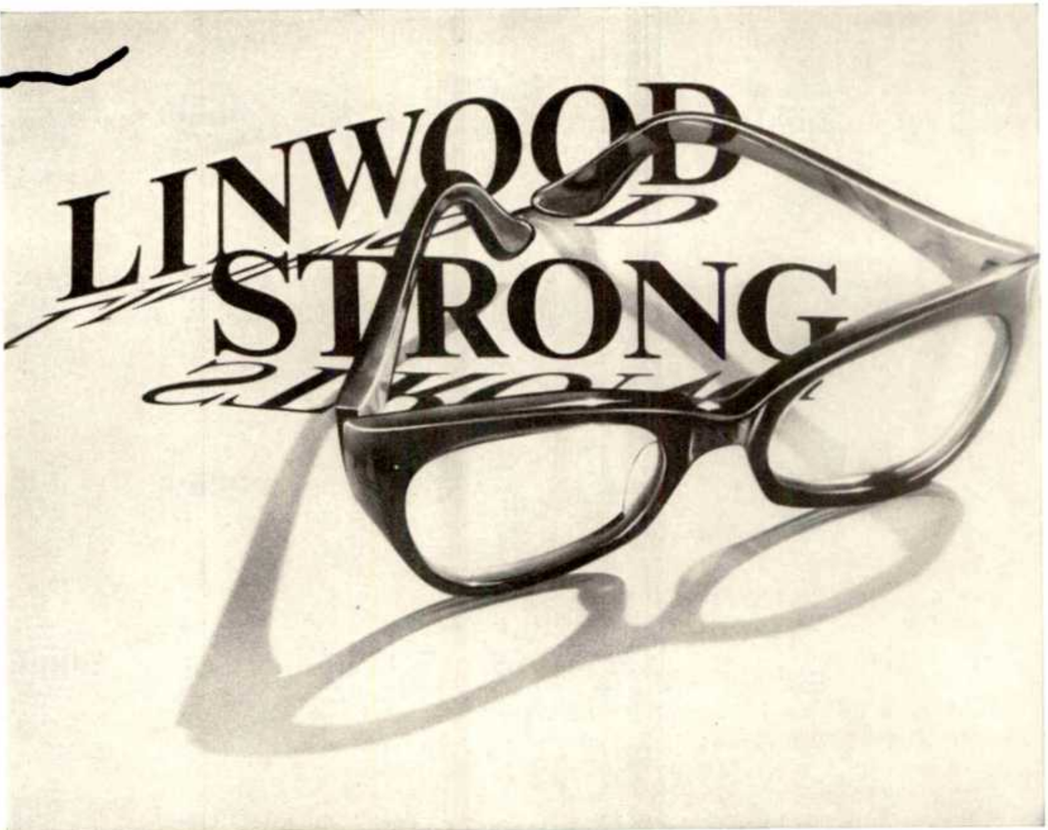

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Atlas of Ophthalmic Surgery

John Harry King, M.D., F.A.C.S., and Joseph A. C. Wadsworth, M.D. *Second Edition*, January 1971. 648 pages, 300 illustrations. Lippincott, £20.00

In reviewing the first edition of this book, the *Transactions of the American Academy of Ophthalmology and Otolaryngology* said 'It is truly a complete surgical atlas and a great contribution to the educational efforts of modern teaching.' It has been out of print for several years, but a completely revised edition has been prepared; it has been brought up to date, largely rewritten and has been enhanced by many new illustrations. The subject matter is presented in fourteen sections and includes surgery of the eyelids, conjunctiva, cornea, lens, iris, retina, extraocular muscles, lacrimal system, orbit and handling of intraocular foreign bodies.

Clinical Neuro-Ophthalmology

Bryan Ashworth, M.D., M.R.C.P. (Lond.), M.R.C.P. (Edin.). Autumn 1971. 500 pages, 100 illustrations (some colour). About £7.00

Diabetes and the Eye

F. I. Caird, D.M., M.R.C.P., A. Pirie, M.A., PH.D. and T. G. Ramsell, M.A., M.D., D.O., F.R.C.S. (Edin.). 1969. 240 pages, 69 illustrations (6 colour). £3.15

Lecture Notes on Ophthalmology

Patrick D. Trevor-Roper, M.A., M.D., B.CHIR. (Cantab.), F.R.C.S., D.O.M.S. (Eng.). *Third Edition*, 1968. 112 pages, 78 illustrations (12 colour). £1.00

General Ophthalmology

Daniel Vaughan, M.D., Robert Cook, M.D. and Taylor Asbury, M.D. *Fifth Edition*, 1968. 328 pages, 246 illustrations. Large, limp £3.15

Cryotherapy of Ocular Diseases

John Bellows, M.D. 1966. 168 pages, 71 illustrations. Lippincott, £6.00

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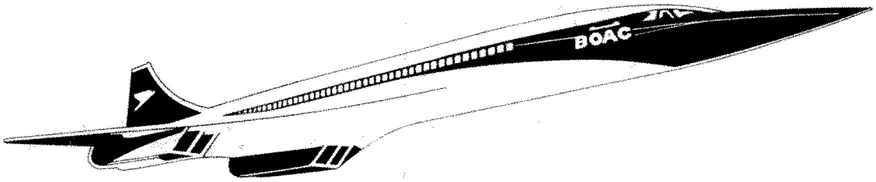

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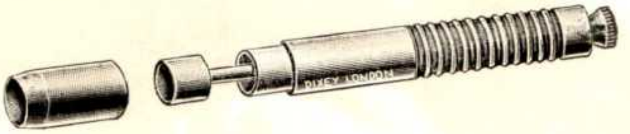

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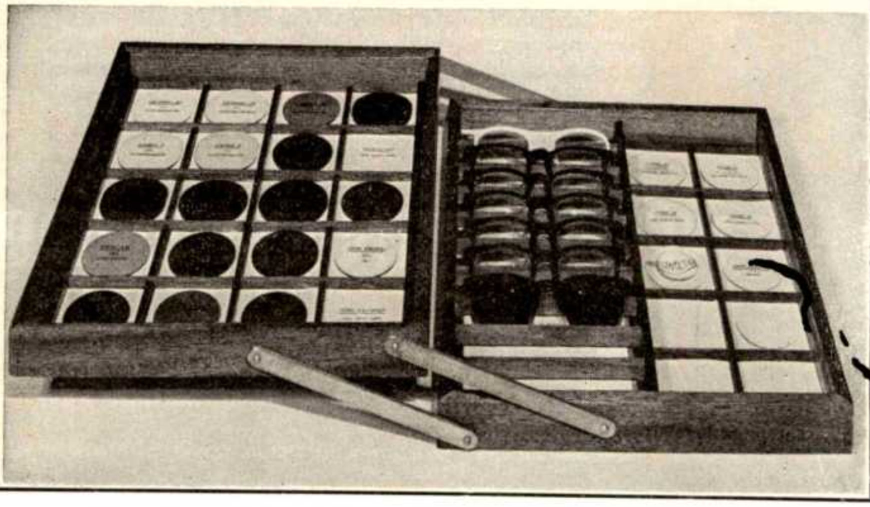

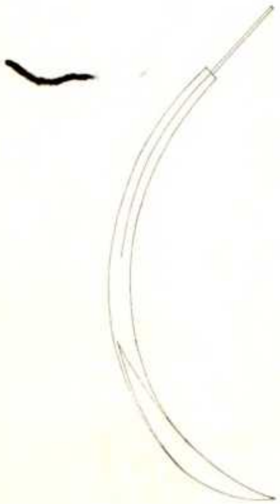

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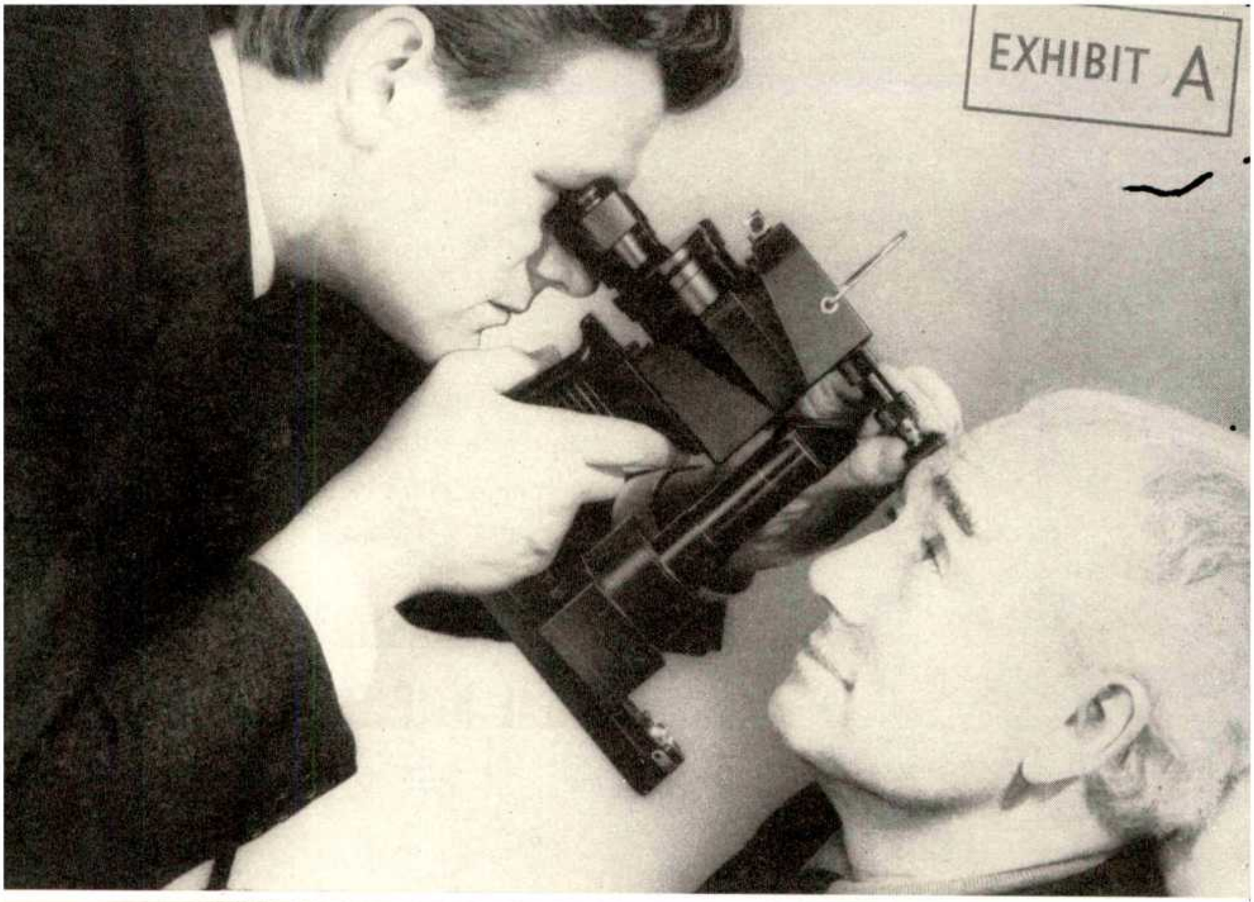
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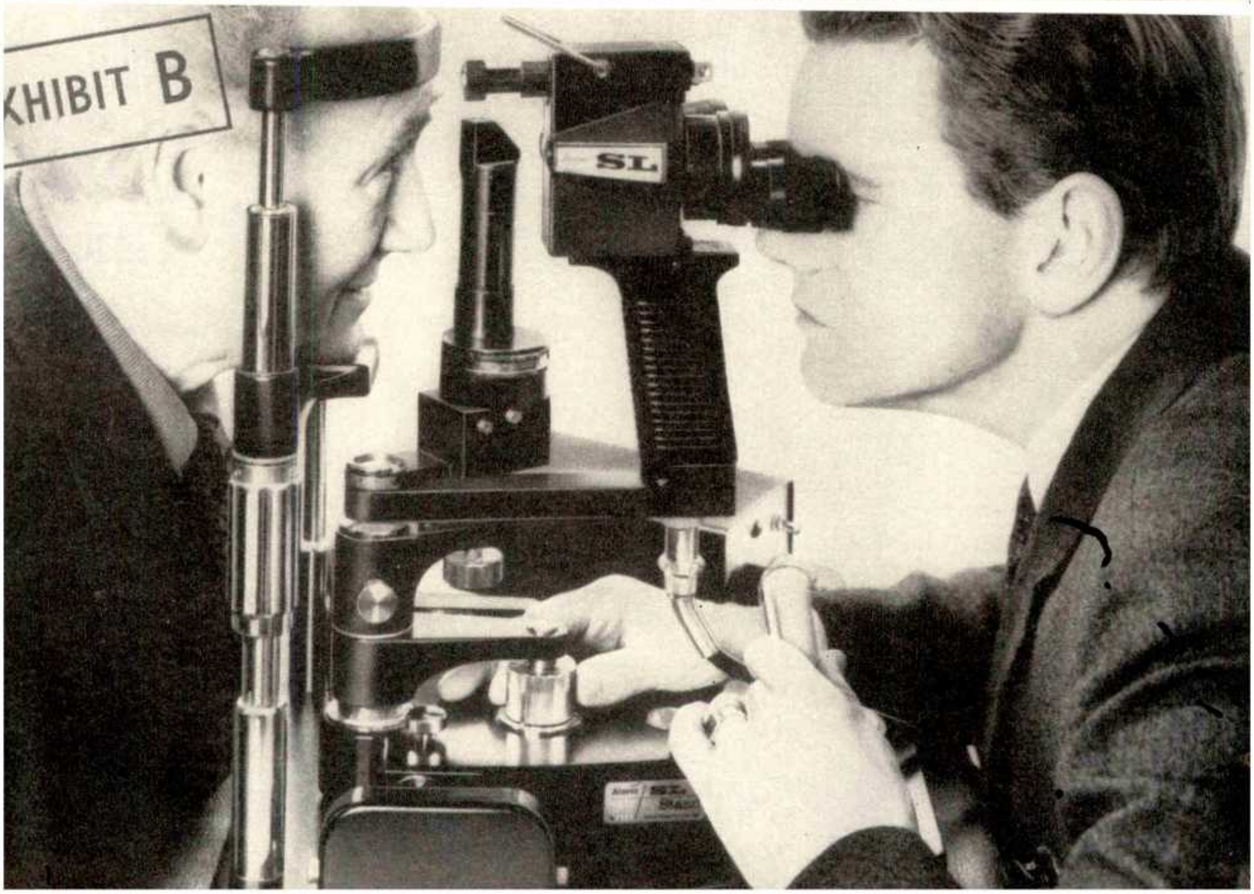
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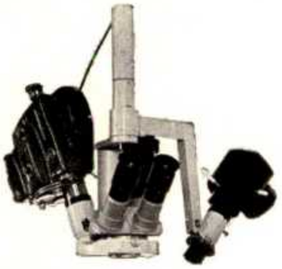

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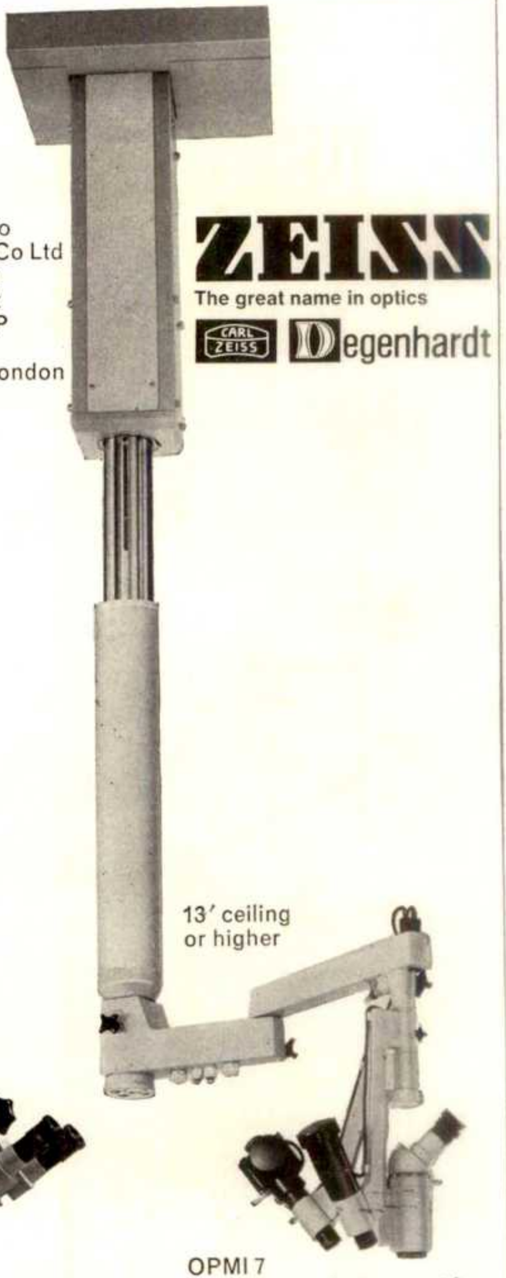

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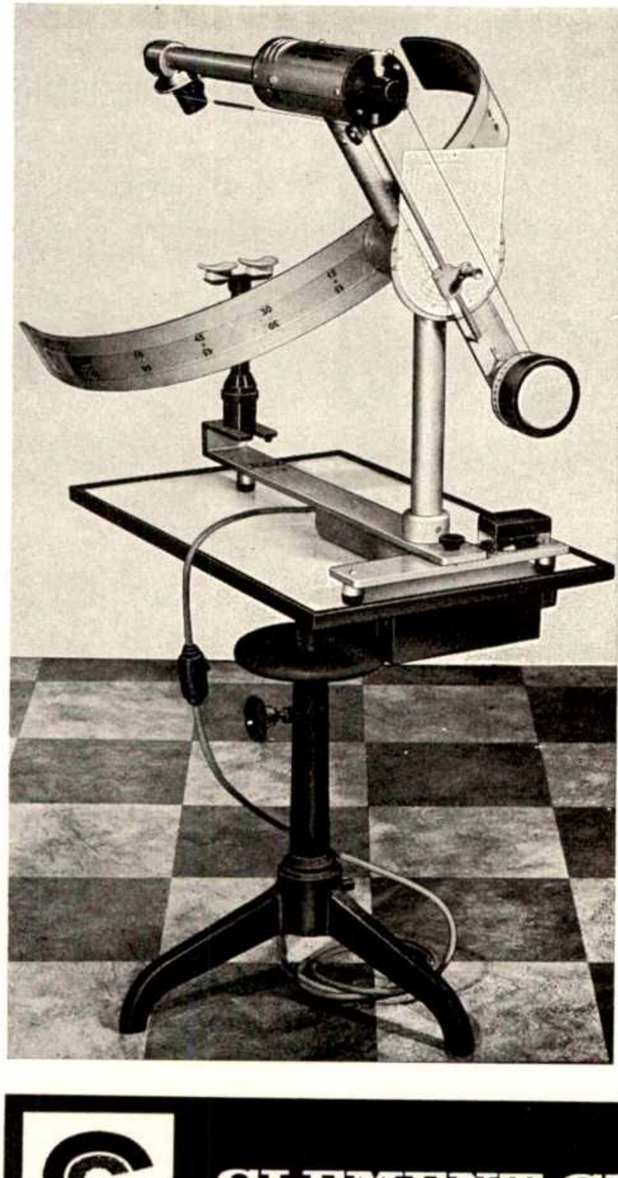

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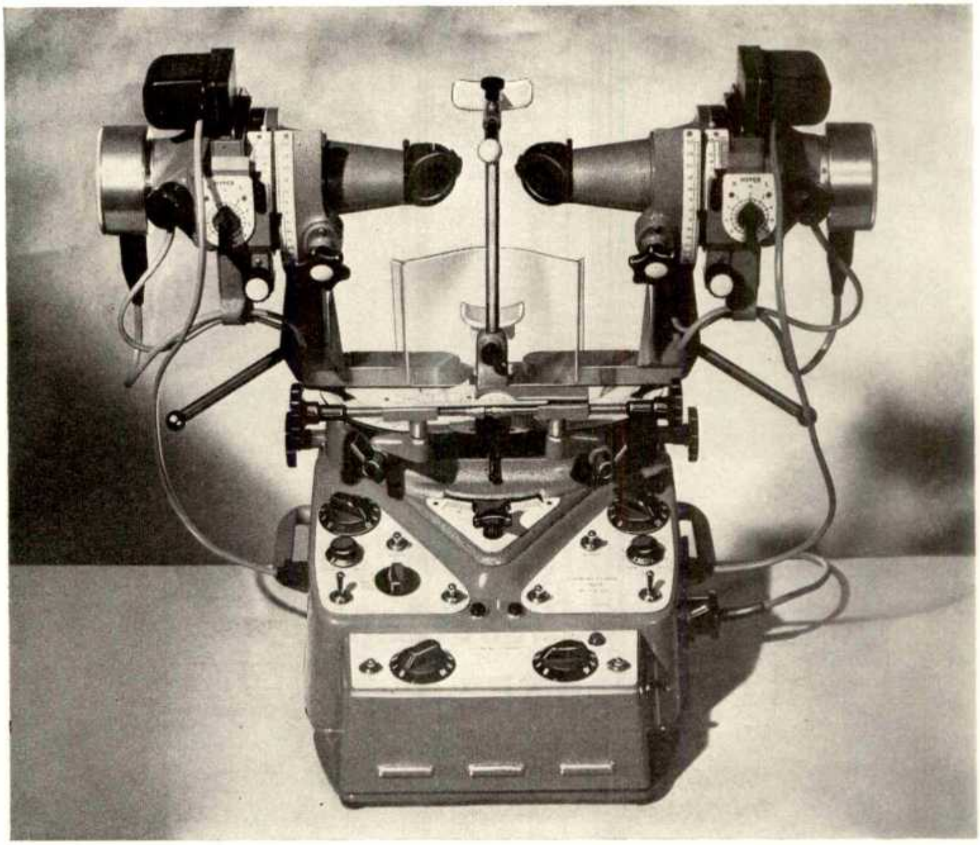

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Communications

Ischaemic optic neuropathy in chronic simple glaucoma

*I. S. BEGG, S. M. DRANCE, AND V. P. SWEENEY

From the Department of Ophthalmology and the Division of Neurology, Department of Medicine, University of British Columbia; the Glaucoma Clinic and Division of Neurology, Vancouver General Hospital; and the Department of Ophthalmology, Shaughnessy DVA Hospital, Canada

The characteristic visual field changes of early glaucoma occur in the Bjerrum area of the visual field and are related to damage of the arcuate nerve fibre bundles (Traquair, 1944; Harrington, 1964a). The susceptibility of these nerve fibre bundles at the optic nerve head to functional changes, whether reversible, relative, or absolute, is the prime characteristic feature of the glaucomatous process, although it is not exclusive to this disease. A vascular cause for this damage has been postulated by many authors (Duke-Elder, 1962; Gafner and Goldmann, 1955; Harrington, 1959; Feldman, Sweeney, and Drance, 1969), but in some instances a metabolic derangement of the neurone may influence its susceptibility to damage from reduction in blood supply (Armaly, 1969).

In previous communications we have described an acute ischaemic change in the optic nerve head characterized by a symptomless haemorrhage on a sector of the disc and a corresponding fresh absolute arcuate scotoma, a sequence of events hitherto not described in chronic simple glaucoma and probably of considerable importance in the natural history of the disease (Drance and Begg, 1970; Begg, Drance, and Sweeney, 1970). The present report amplifies the concept of ischaemic optic neuropathy in the glaucomatous process and shows that it can be responsible in some eyes for the conversion of ocular hypertension to chronic simple glaucoma.

Material and methods

The seven cases were selected from a group of over thirty patients as typical examples. In addition to full ophthalmological evaluation, the general assessment consisted of an examination by a vascular neurologist, and the following additional investigations were carried out:

(1) Full blood count, erythrocyte sedimentation rate, packed cell volume
(2) Serum electrolytes, cholesterol, plasma proteins, blood urea nitrogen
(3) Serum P.B.I., T_4 by column
(4) Fasting blood sugar and 2 hrly p.c.
(5) Glucose tolerance test in selected patients
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(8) Electrocardiogram
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*In receipt of University of British Columbia Teaching Fellowship

Case reports

Case 1, a 55-year-old man, was found to have chronic simple glaucoma in 1963 with intraocular pressures of 31 mm.Hg in both eyes. He was slightly myopic with normal visual acuity. There was a family history of glaucoma on his mother's side. Gonioscopy revealed a wide open angle with a heavy pigmentation. The coefficient of outflow facility on therapy was 0·19 in both eyes.

Examination in 1965 showed that the right disc was pale and pathologically cupped and that the left disc was suspiciously cupped. Visual field examination showed a lower arcuate scotoma in the right eye and a full field in the left eye. He was treated with miotics, epinephrine, and Diamox, but the latter was discontinued in 1966 when renal calculi developed. Despite the fact that the treated ocular tension rose only to 20 mm.Hg in the right eye and 18 mm.Hg in the left, an upper paracentral scotoma developed in the right eye and a lower absolute scotoma adjacent to the horizontal meridian in the inferior Bjerrum area in the left. Field loss continued during the next 2 years.

In 1968, the tension rose to 25 mm.Hg in both eyes and a Scheie's operation was carried out in the right eye; but 4 months later therapy was resumed.

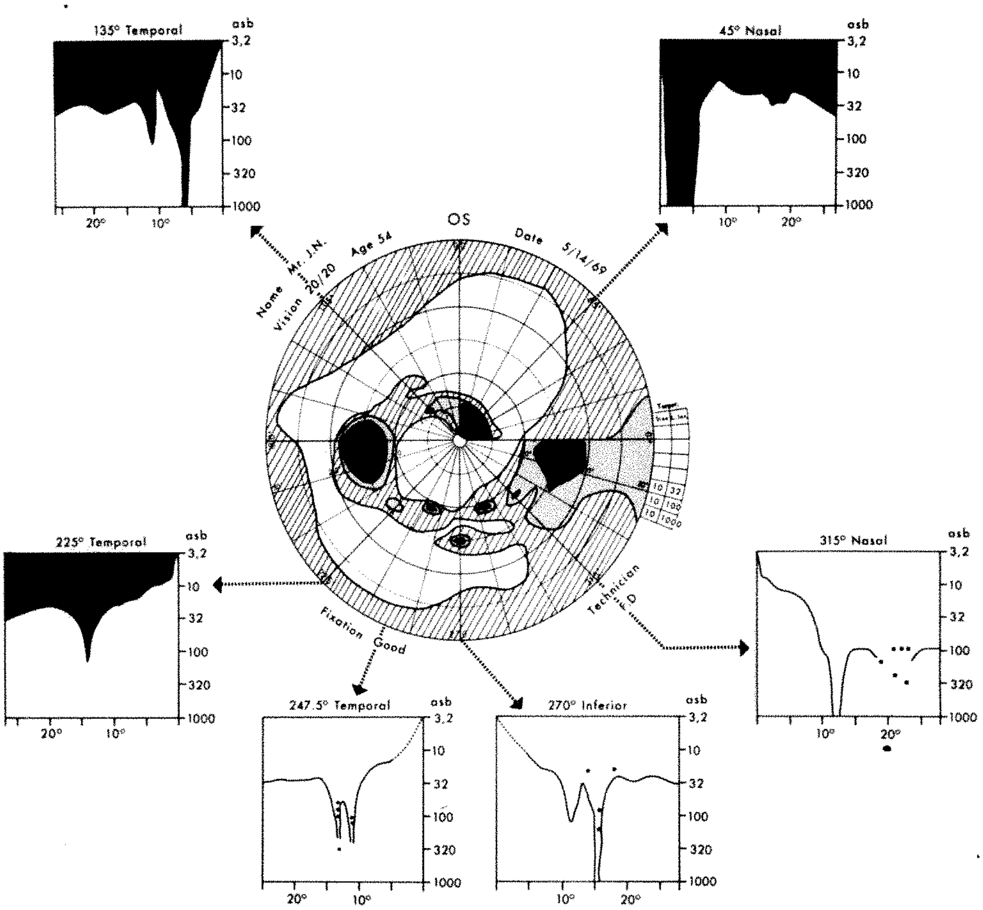

FIG. 1 *Case 1. Static and kinetic field, showing superior arcuate scotoma with absolute paracentral nucleus in the nasal quadrant, and inferior arcuate scotoma with multiple absolute nuclei*

A general assessment in 1968 showed that the patient was in good general health and that there were no signs of diabetes, or evidence of cardiac, cerebrovascular, or peripheral vascular insufficiency. No bruits over the internal carotid arteries were heard, but the blood pressure was only 110/76.

The visual field of the left eye in May, 1969, is shown in Fig. 1. In October, 1969, a linear haemorrhage at 5 o'clock on the neuroretinal rim of the left disc was observed. The cup:disc ratio was 0·6 in the right eye and 0·7 in the left. Static field examination of the left eye showed a slight extension of the superior absolute nucleus as well as a fresh scotoma inferiorly, adjacent to the horizontal meridian, extending peripherally from the 20° isopter (Fig. 2). The intraocular pressures in the preceding months had varied from 20 to 28 mm.Hg.

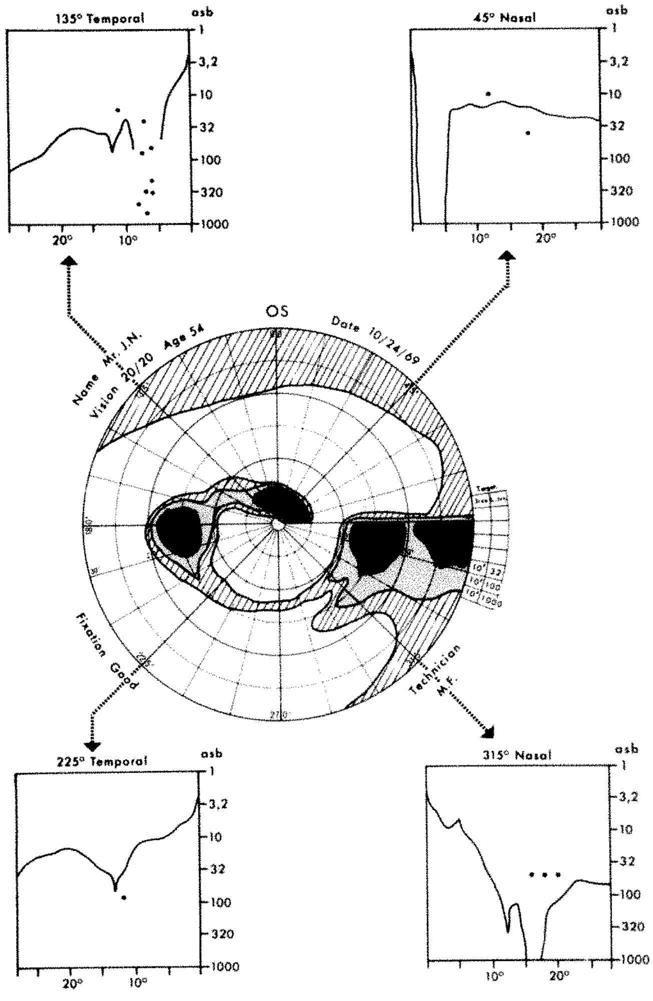

FIG. 2 *Case 1. Static and kinetic field, showing fresh extension of absolute nucleus in superior arcuate scotoma, and fresh absolute scotoma inferiorly adjacent to horizontal meridian*

Case 2, a 67-year-old woman, was seen in October, 1968, with a history of chronic simple glaucoma of at least 4 years' duration. Her highest intraocular pressures were 30 mm.Hg in both eyes. There was a family history of glaucoma. A drainage procedure had been carried out in the right eye in 1965 and the intraocular pressure thereafter remained within the normal range, although lens opacities and postinflammatory adhesions had developed so that the right disc could not be seen. The left eye had been treated with 4 per cent. pilocarpine and Diamox with a diurnal tension peak up to 22 mm.Hg. The outflow coefficient in the left eye was 0·13, Po/C = 154. There was deep excavation of the left disc, and a markedly narrowed inferior neuroretinal rim. The retinal arterioles showed marked irregularity and calibre variation, and there were arterio-venous crossing changes.

Static field examination of the left eye in October, 1968, showed a relative superior paracentral scotoma in the nasal field (Fig. 3).

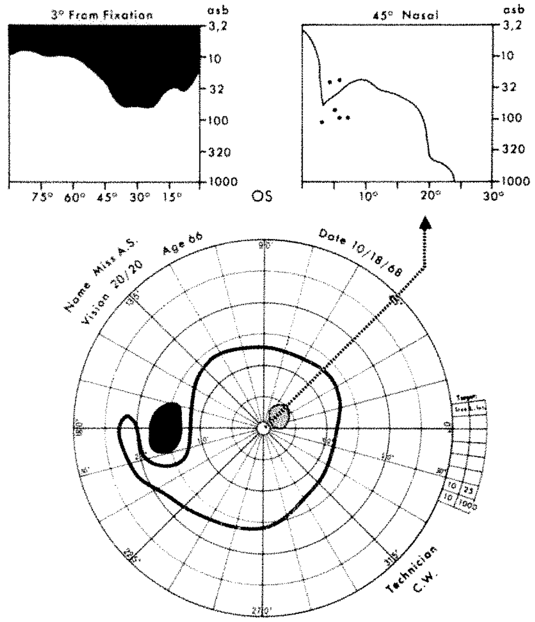

FIG. 3 *Case 2. Static and kinetic field, showing relative paracentral scotoma close to fixation*

A general assessment revealed that she had received intermittent treatment for mild hypertension since 1942, but not during the period of ocular examinations. There was no history of cardiac ischaemia or peripheral vascular disease. In the past, she had experienced recurrent paroxysmal tachycardia in association with syncopal episodes but no attacks had occurred recently. On one occasion it was recorded that the blood pressure could not be measured at the time of the tachycardia. There was a past history of hysterectomy for malignancy, and cholecystectomy, but without hypotension on either occasion. Her blood pressure was 170/90. There was evidence of left ventricular enlargement. The internal carotid arteries had normal pulsation and no bruits.

In May, 1969, a superficial, flame-shaped haemorrhage was observed in the 5 o'clock position on the neuroretinal rim of the left optic disc. The cup:disc ratio was 0·9 and the neuroretinal rim was almost transparent and virtually non-existent at 5 to 6 o'clock. Marked peripapillary atrophy surrounded the disc. The intraocular pressures were 12 mm.Hg in the right eye and 20 mm.Hg in the left. Visual field examination showed an extension of the superior arcuate scotoma with a fresh small absolute nucleus. A fresh absolute scotoma in the inferior field was also present (Fig. 4). Treatment was changed to include phospholine iodide 0·125 per cent., epinephrine 2 per cent., and Diamox, and on this regime the intraocular pressures were reduced to 10 mm.Hg in the right eye and 15 mm.Hg in the left, the outflow coefficients being 0·29, Po/C = 34 in the right eye and 0·27, Po/C = 74 in the left.

Another superficial haemorrhage was observed 3 months later at the left disc, overlying the neuroretinal rim and adjacent retina at 6 o'clock (Fig. 18). Visual field examination of the left eye showed a marked deterioration, as the absolute nucleus of the superior arcuates cotoma had increased considerably, and there was also a fresh absolute scotoma superiorly in the Bjerrum area (Fig. 5, overleaf). The intraocular pressure on this occasion was 16 mm.Hg in the right eye, but it had risen to 26 mm. Hg in the left.

An external trabeculectomy was carried out on the left eye in October, 1969, and the intraocular pressure has since remained well within the normal range. In March, 1970, a flame-shaped haem-

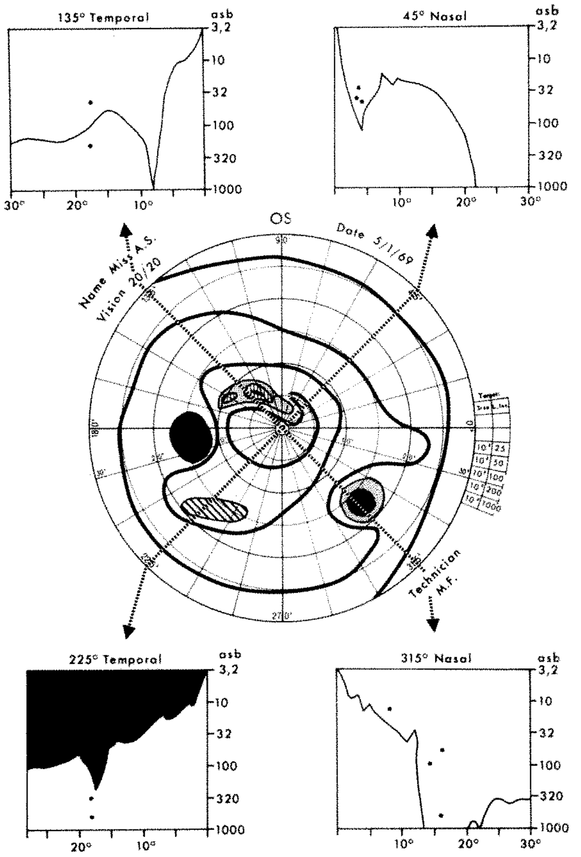

FIG. 4 *Case 2. Static and kinetic field, showing fresh extension of superior arcuate scotoma with development of absolute nucleus; also fresh absolute scotoma in infero-nasal quadrant*

orrhage was noted at 2.30 o'clock on the rim of the left disc. Visual field examination showed no fresh defect. The diurnal tension peak was 17 mm.Hg.

A general assessment was repeated in 1970. There were no specific symptoms of vascular disease and no change in the patients physical state was observed. The blood pressure was 190/106.

Case 3, a 56-year-old woman, was found to have chronic open-angle glaucoma in December, 1966. The intraocular pressures were 26 mm.Hg in the right eye and 30 mm.Hg in the left, with widely open angles. Cupping of the optic discs was asymmetrical, the left being greater than the right. Visual field examination with the Goldmann perimeter revealed two small relative paracentral scotomata in the superior Bjerrum area of the left eye to a 1/2 target. There was no family history of glaucoma.

Intraocular pressure levels were maintained, on the whole, just below 21 mm.Hg on therapy. No progression of the visual field defect was observed. In fact, repetition showed the disappearance of the relative defects in 1967. The relative paracentral scotomata were again demonstrated in 1968 to a 1/2 target.

In June, 1969, a superficial linear haemorrhage was observed at the margin of the left disc. It was situated at the 5 o'clock position, where the neuroretinal rim was narrowed and excavated. The cup: disc ratio was 0·6 in the right eye and 0·8 in the left. There was no significant peripapillary atrophy. The retinal arterioles were narrowed and straightened. Static field examination showed an absolute arcuate scotoma (Fig. 6). The intraocular pressures at this time were 19 mm.Hg in

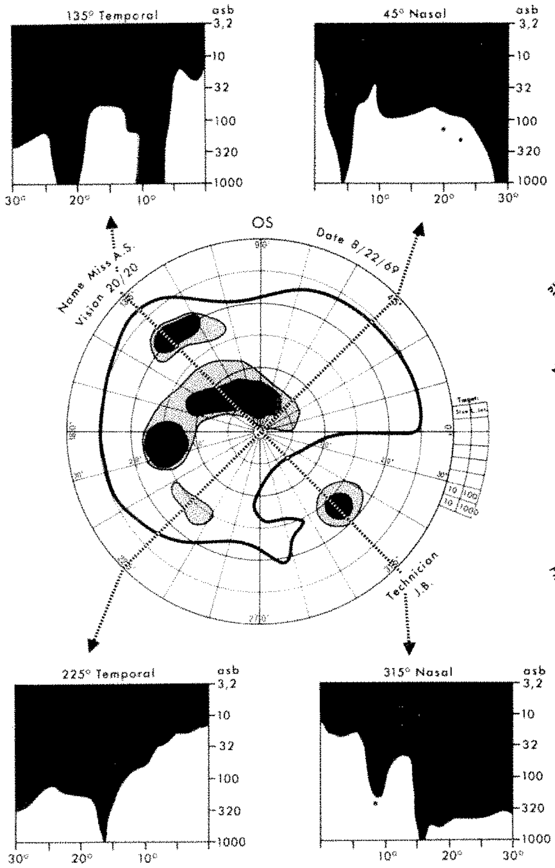

FIG. 5 *Case 2. Static and kinetic field, showing considerable fresh extension of absolute nucleus of superior arcuate scotoma, and fresh absolute scotoma superiorly in Bjerrum area*

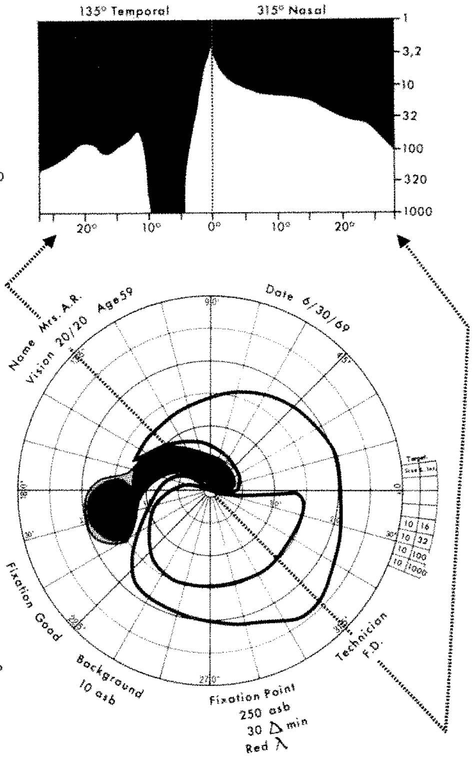

FIG. 6 *Case 3. Static and kinetic field, showing fresh absolute arcuate scotoma*

the right eye and 22 mm.Hg in the left. A month later there was no sign of the haemorrhage but a local atrophy of the neuroretinal rim was observed.

In 1967 the patient underwent mastectomy for breast malignancy and that same year she first experienced occasional mild angina of effort, aggravated by anaemia which was successfully treated. She had experienced episodes of pain above the left eye, attributed to sinusitis and successfully treated by antral lavage. No internal carotid bruit was detected. The blood pressure was 160/90. There had been no recent changes in her general medication. Repeated electrocardiograms showed sinus rhythm and severe left bundle branch block, indicating changes which suggested that myocardial infarction had occurred in August and October, 1969.

Case 4, a 64-year-old woman, who had been examined yearly for presbyopic correction since 1963, was found to have a symptomless haemorrhage on the left optic cup in July, 1965. The intraocular pressures were 28 mm.Hg in the right eye and 26 mm.Hg in the left. Gonioscopy revealed wide open angles. Tangent field examination showed full fields. There was no family history of glaucoma. Treatment with 2 per cent. pilocarpine was started, but this was later changed to 4 per cent. pilocarpine, as the intraocular pressures ranged between 20 and 26 mm.Hg.

In March, 1968, the right disc was physiologically cupped and there was excavation and atrophy of the neuroretinal rim of the left disc at 5 to 6 o'clock. There was moderate bilateral peripapillary atrophy. The retinal arterioles showed sclerotic changes. A visual field examination showed a full field in the right eye and an absolute superior arcuate-shaped paracentral scotoma in the left (Fig. 7).

The intraocular pressures remained within the normal range on therapy, but in August, 1969, a fresh haemorrhage was observed at the left disc. It was partly superficial, partly deep, and was situated on the neuroretinal rim at 2 o'clock (Fig. 8).

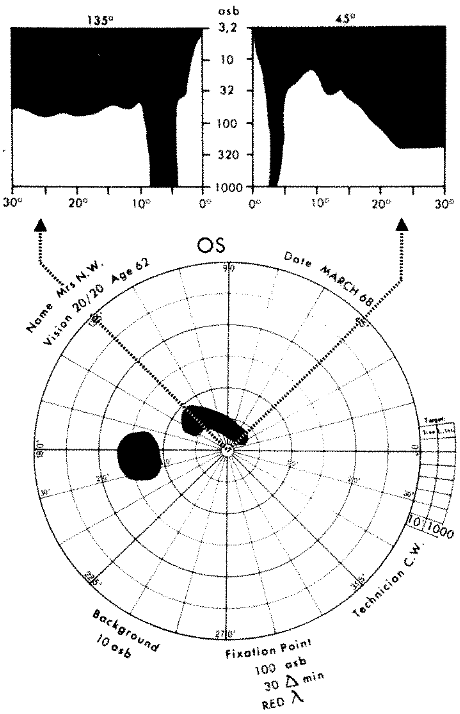

FIG. 7 *Case 4. Static and kinetic field, showing absolute arcuate-shaped paracentral scotoma*

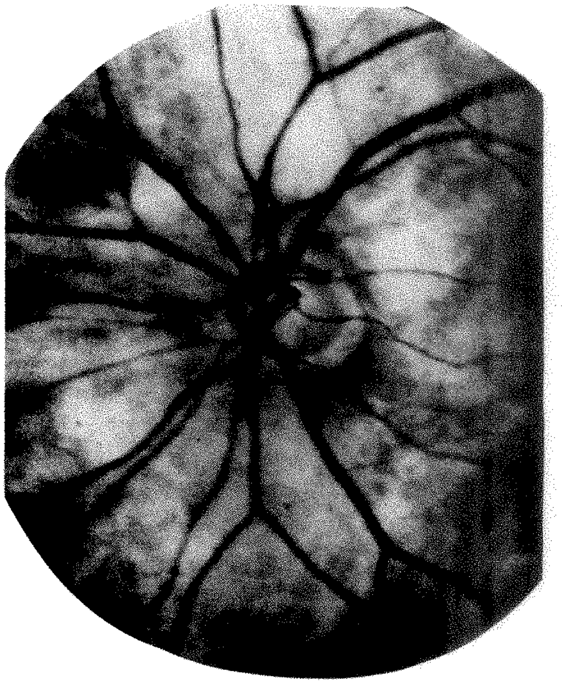

FIG. 8 *Case 4. Left optic disc, showing a haemorrhage on the neuroretinal rim at 2 o'clock*

Static visual field examination showed a fresh inferior arcuate-shaped scotoma with an absolute nucleus (Fig. 9, overleaf).

In February, 1970, a superficial haemorrhage was observed at the right optic disc, situated at 6.30 o'clock on the neuroretinal rim, which was otherwise pink and regular. Static visual field examination showed a small superior relative paracentral scotoma (Fig. 10) with a small nasal step in the more peripheral isopter (Fig. 11, overleaf).

A general assessment in 1970 revealed a past history of mild hypertension which had been treated for several years, but she was receiving no medication at the time of the ocular examinations. Her blood pressure was 150/90. There was a past history of peptic ulcers. A glucose tolerance test was positive. A platelet adhesiveness test was 77 per cent. (normal range 20 to 60 per cent.), consistent with a hypercoagulable state.

SUMMARY

These four patients demonstrate the extension of existing glaucomatous defects or the occurrence of fresh defects in glaucomatous eyes accompanied by discrete linear haemorrhages on the optic nerve head.

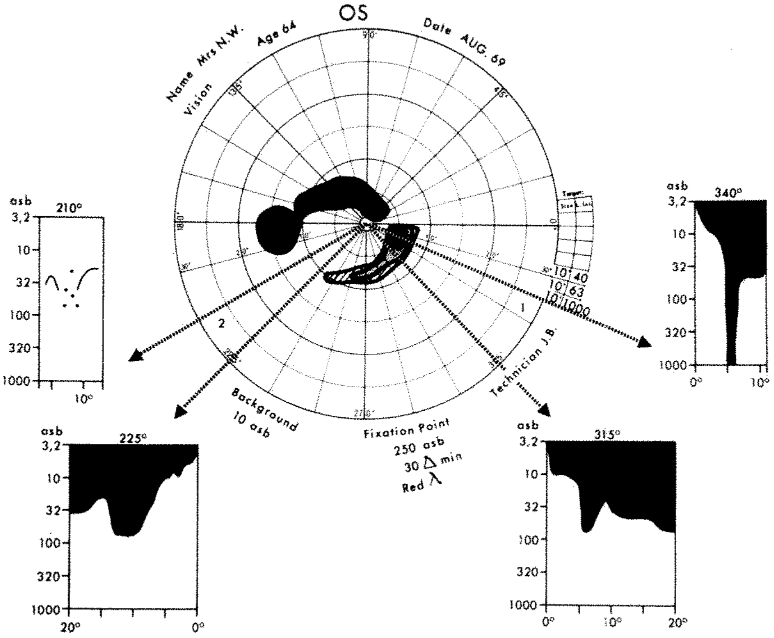

FIG. 9 *Case 4. Static and kinetic field, showing fresh inferior arcuate scotoma with absolute nucleus*

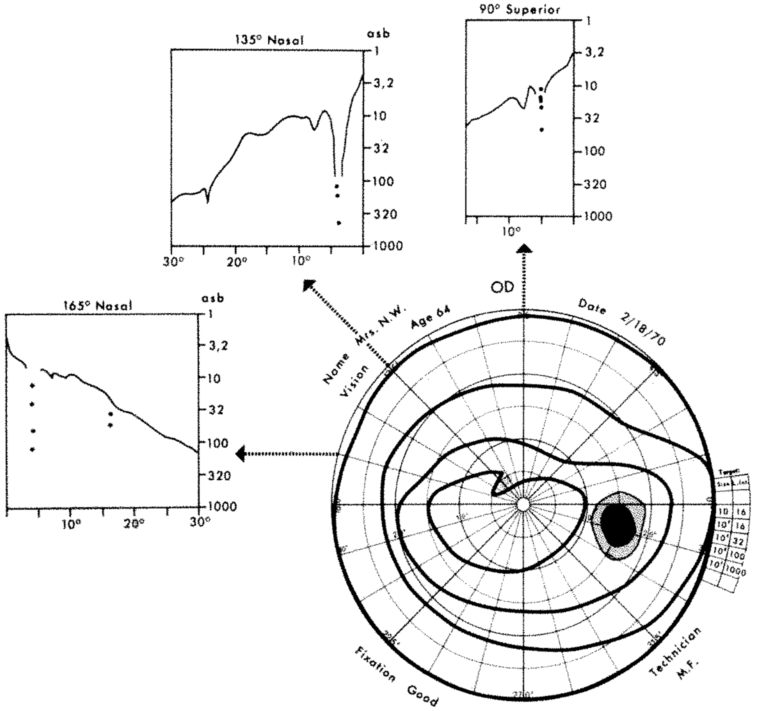

FIG. 10 *Case 4. Static and kinetic field, showing fresh, small, relative paracentral scotoma close to fixation*

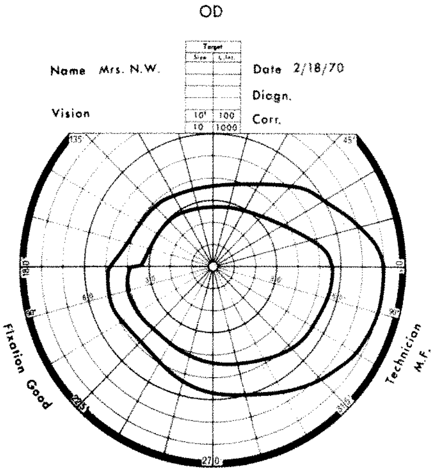

FIG. 11 *Case 4. Peripheral kinetic field, showing associated small nasal step (see Fig. 10)*

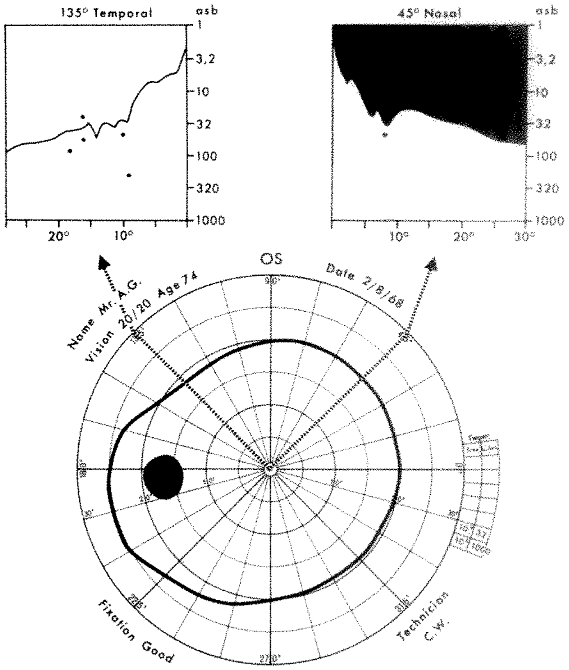

FIG. 12 *Case 5. No field defect demonstrated by kinetic and static perimetry*

Case 5, a 76-year-old man, attended for refraction in December, 1967, when ocular hypertension was first discovered. There was no family history of glaucoma. His mother had had a stroke when 40 years old. The intraocular pressures were 22 mm.Hg in both eyes and the coefficient of outflow facility was 0·19 in the right eye and 0·29 in the left. Gonioscopy revealed wide open angles. Both optic discs showed wide physiological cupping. Static and kinetic visual field examination in February, 1968, revealed no defects (Fig. 12). At subsequent examinations during the next 10 months the intraocular pressures, untreated, ranged from 17 to 25 mm.Hg in both eyes.

In October, 1968, an appearance of "neovascularization" was seen at 5 o'clock on the left optic disc. Static perimetric examination 2 months later showed an unusual relative paracentral scotoma in the superior Bjerrum area of the left eye (Fig. 13, overleaf). The visual field in the right eye remained intact. The intraocular pressures were maintained at about 15 mm.Hg on a regime of 2 per cent. pilocarpine to both eyes.

A general assessment in January, 1969, revealed no cerebrovascular or peripheral vascular symptoms apart from occasional "drop" attacks without loss of consciousness, which were attributed to probable impairment of the basilar system. There were no neurological symptoms. The blood pressure varied between 140/80 and 160/90, without postural hypotension. A glucose tolerance test showed no abnormality. An electrocardiogram showed left ventricular hypertrophy and an old anterior septal myocardial infarction.

In March, 1969, there was no sign of "neovascularization" but a flame-shaped haemorrhage was noted on the left disc. The arterioles showed sclerotic changes in both eyes. A month later a fresh haemorrhage was observed on the right disc at 5 o'clock. Visual field examination in May, 1969, showed the appearance of a fresh absolute nucleus in the superior paracentral scotoma in the left eye, and a fresh absolute scotoma inferiorly adjacent to the horizontal meridian (Fig. 14, overleaf) but no field change in the right eye.

In October, 1969, the right optic disc remained unchanged, but marked notching of the neuroretinal rim of the left disc was noted at 1 and 5 o'clock. The cup:disc ratio was 0·7 in both eyes.

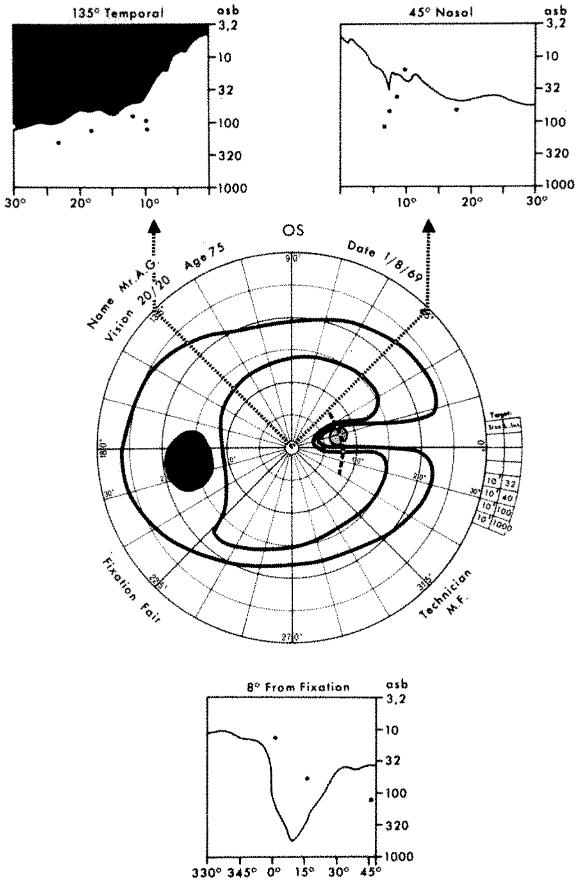

FIG. 13 *Case 5. Relative paracentral scotoma above nasal horizontal meridian*

Visual field examination showed a fresh absolute nucleus in the left eye, situated adjacent to the horizontal meridian 30J from fixation (Fig. 15, overleaf).

Another fresh haemorrhage at the right optic disc was noted in December, 1969. It was situated partly on the transparent neuroretinal rim and partly on the adjacent choroidal crescent at 5.30 o'clock. Static perimetric examination showed a small fresh absolute paracentral scotoma in the 90° meridian, 14° isopter of the superior Bjerrum area. Diamox was added to the local therapy. In April, 1970, a fresh haemorrhage was noted at 5.30 o'clock on the margin of the right disc, and there was marked narrowing of the rim at this site. Static perimetric examination of the right eye revealed a fresh small absolute scotoma in the 175° meridian, with a small nasal step, as well as a peripheral depression in the 150° meridian.

Case 6, a 73-year-old woman, had mild ocular hypertension which was first detected in 1964 when the intraocular pressures were 22 mm.Hg in the right eye and 20 mm.Hg in the left. There was no family history of glaucoma. Gonioscopy revealed narrow open angles, with a plateau iris appearance. There was wide, deep physiological cupping of both optic discs and the visual fields were full. The coefficient of outflow facility, untreated, was 0·13 in the right eye and 0·17 in the left. A water-drinking test was positive. The intraocular pressures fluctuated between 20 and 25 mm.Hg thereafter, and a gradual reduction in visual acuity took place due to lens opacities.

In June, 1967, a flame-shaped haemorrhage was observed infero-temporally on the left disc, but static visual field examination showed no defect. In May, 1968, the treated diurnal tension peaks were 20 mm.Hg in both eyes and the optic discs remained unchanged.

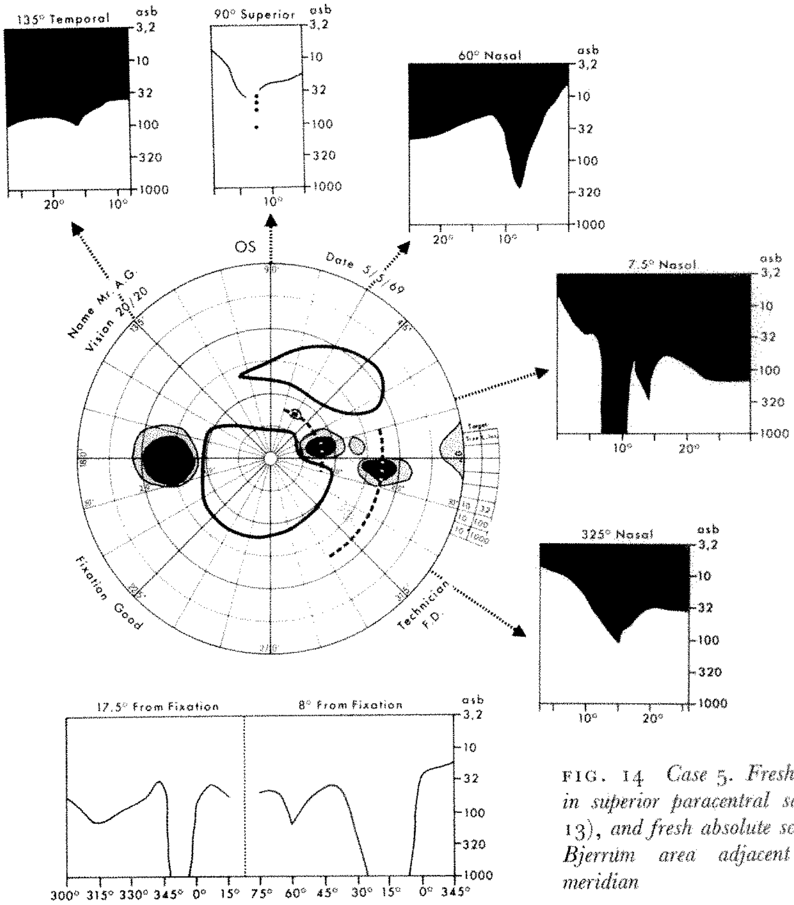

FIG. 14 *Case 5. Fresh absolute nucleus in superior paracentral scotoma (see Fig. 13), and fresh absolute scotoma in inferior Bjerrum area adjacent to horizontal meridian*

In March, 1970, a superficial haemorrhage was observed at the left disc, at 5 o'clock overlying the neuroretinal rim and peripapillary region. The right optic disc remained unchanged. The cup: disc ratio was 0·8 in the right eye and 0·7 in the left. There was no significant peripapillary atrophy. The arterioles showed slight sclerotic changes in both eyes. Static field examination revealed a small relative paracentral scotoma situated in the 2° meridian, 34° from fixation, and a nasal step (Fig. 16). At this time the diurnal tension peaks on therapy were 18 mm.Hg in the right eye and 17 mm.Hg in the left.

General assessment revealed no significant past history. There were no cardiovascular, cerebrovascular, or neurological symptoms or signs. The blood pressure was 170/90 with no postural change. Repeated electrocardiograms showed evidence of an old atrio-septal myocardial infarct, unchanged since 1967. The erythrocyte sedimentation rate was 49 mm. in 1 hour. A temporal artery biopsy showed no pathological changes of temporal arteritis.

Case 7, a 72-year-old man with marked myopia, was found to have ocular hypertension in 1964. The intraocular pressures were 30 mm.Hg in the right eye and 35 mm.Hg in the left. Gonioscopy revealed wide open angles. The optic discs showed suspicious cupping, but careful tangent screen visual field examination to 1/1000 white target showed no defect. There was no family history of glaucoma. Initially, good control was achieved on 2 per cent pilocarpine, but additional therapy, including Diamox, became necessary. Control was erratic and in May, 1969, the diurnal tension peaks were 35 mm.Hg in the right eye and 29 mm.Hg in the left. The optic discs were unchanged and static and kinetic visual field examination showed no defects.

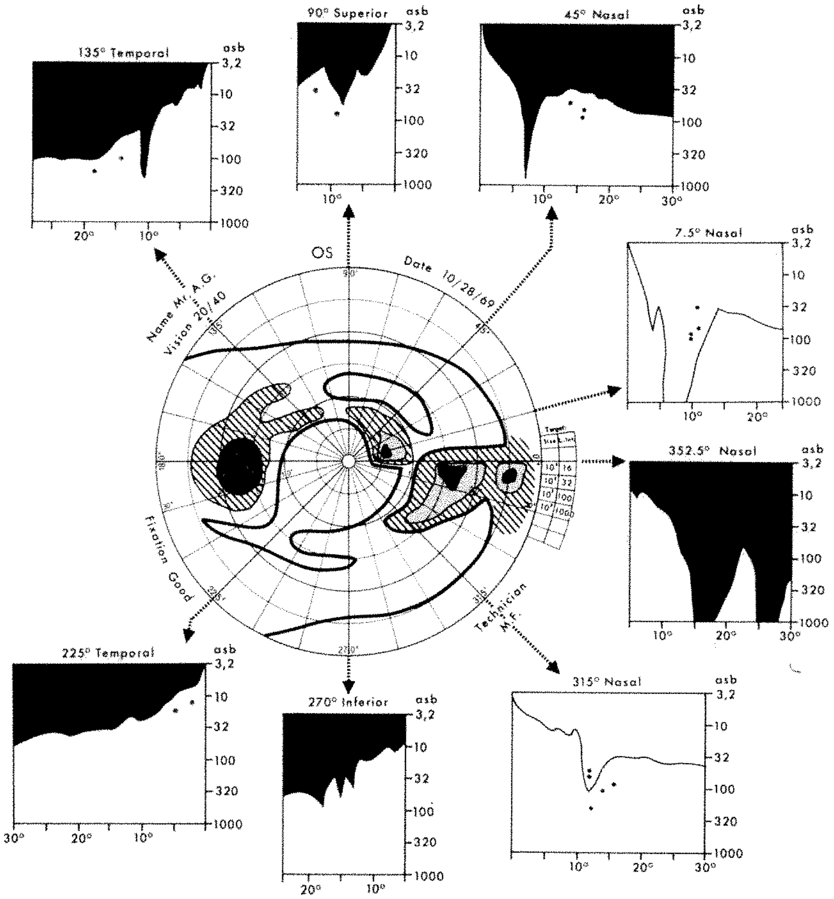

FIG. 15 *Case 5. Fresh absolute nucleus adjacent to horizontal meridian in 30° isopter*

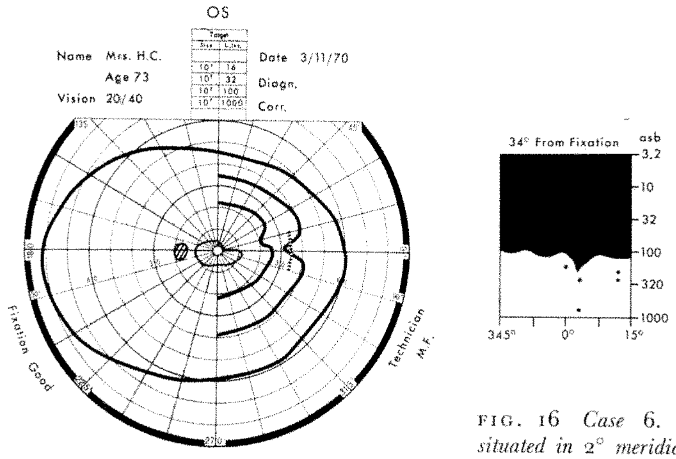

FIG. 16 *Case 6. Small relative paracentral scotoma situated in 2° meridian, 34° from fixation seen in circular static perimetry accompanied by nasal steps in smaller isopters*

In January, 1970, examination showed that there was saucerization and transparent change in both optic discs which were surrounded by marked peripapillary atrophy. In the left disc there was a minute, deep haemorrhage in the neuroretinal rim at 2.30 o'clock. The intraocular pressures at this time were 26 mm.Hg in the right eye and 22 mm.Hg in the left. Static field examination of the left eye showed a lower nasal step in the central and peripheral isopters (Fig. 17).

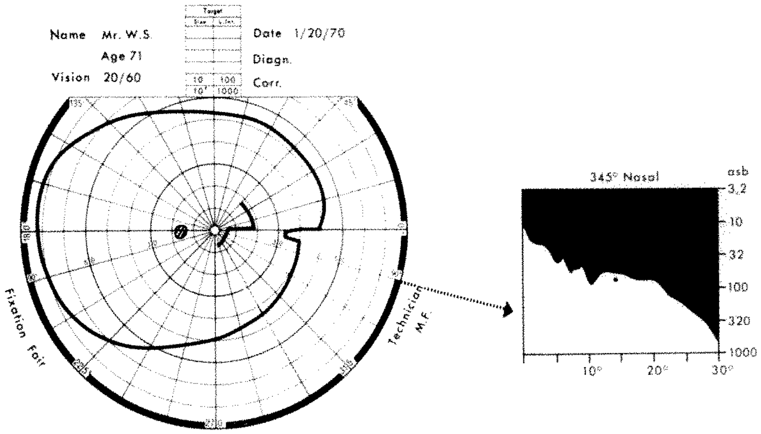

FIG. 17 *Case 7. Lower nasal step in central and peripheral isopters*

General assessment revealed no significant past history and no symptoms of vascular or neurological disease. The blood pressure was 136/76 with no postural change. The pulse was 68/min. and ment lting. Aortic stenosis and mitral insufficiency were detected with moderate cardiac enlarge- fibrialbut no definite evidence of congestive heart failure. Systolic bruits were present over both internal carotid arteries, possibly conducted from the heart. The electrocardiogram showed a rapid ventricular rate with frequent premature ventricular contractions.

SUMMARY

These three patients showed ocular hypertension in which haemorrhages at the disc were accompanied by visual field defects of varying degree ranging from relative to multiple absolute defects heralding the change from ocular hypertension to chronic simple glaucoma.

Summary of findings

Some characteristics were shared by this group of patients. Three of them, at the outset, were classified as ocular hypertensives with intraocular pressures greater than 21 mm.Hg, physiologically cupped optic discs, and full visual fields assessed by both static and kinetic perimetry. After the initial appearance of a haemorrhage in a sector of the disc, a corresponding nerve fibre bundle defect was plotted and the clinical diagnosis was changed to chronic simple glaucoma. Similar appearance of haemorrhages in sectors of the disc characterized the progression of chronic simple glaucoma in four patients.

The relevant features of these seven cases are listed in the Table (overleaf). Their ages ranged from 55 to 76 years, and a family history of glaucoma was present in two of them. The highest intraocular pressures recorded were well above the statistical limits of normality. The coefficients of outflow facility, when measured, were in the low range, even when recorded under medication. At the time when the disc haemorrhage was observed, the intraocular pressure in this group of patients was either within the normal limits or only

Table *Ischaemic optic neuropathy in chronic simple glaucoma*

Case no.	*Age (yrs)*	*Sex*	*Highest intraocular pressure*		*Cup : Disc ratio R : L*		*Blood pressure*	*Efficient gradient*	*Systemic disease*	*Figures*
			Right	*Left*						
*1	55	M	31	31	0·6	0·7	110/76	34 30	Hypotension	1 and 2
*2	67	F	30	30	0·8	0·9	190/106	— 87	Hypertension Paroxysmal tachycardia	3–5, 18
3	56	F	26	30	0·6	0·8	160/90	76 74	Myocardial infarcts	6
4	64	F	28	26	0·7	0·7	150/90	73 77	Past history of peptic ulcer Glucose tolerance test positive Hypercoagulable state	7–11
5	76	M	25	25	0·7	0·7	160/90	65 72	Myocardial infarction Basilar artery insufficiency	12–15
6	73	F	25	25	0·8	0·7	170/90	81 78	Myocardial infarction	16
7	72	M	35	35	0·7	0·7	136/76	53 32	Aortic stenosis Mitral insufficiency Fibrillating pulse	17

* Family history of glaucoma

slightly elevated. A comparison of the cup: disc ratios showed that the wide cupping was approximately equal in both eyes. A high incidence of moderate to marked peripapillary atrophy was observed. The erythrocyte sedimentation rate was recorded in six of the seven patients and no significant elevation was found. A temporal artery biopsy was carried out on one patient (Case 6) and the histological examination showed no evidence of giant cell arteritis. Evidence of vascular disease was seen in six of the seven patients; hypertension and ischaemic heart disease predominated. One of the patients had a positive glucose tolerance test and increased platelet adhesiveness. The only patient without significant vascular disease had a family history of glaucoma and a low blood pressure.

DESCRIPTION OF HAEMORRHAGE ON A SECTOR OF THE DISC

The disc haemorrhages observed were either superficial or deep, the former appearing to predominate. The superficial haemorrhages were characteristically linear or flame-shaped and spread into the peripapillary retina. Some of these haemorrhages were very fine and could easily have been mistaken through the small pupil for a congested blood vessel, dilated capillaries, or neovascularization. Deep haemorrhages were round and irregular in shape, probably because of the directional change of the nerve fibres on the disc. Deep haemorrhages were occasionally observed in the peripapillary region. The haemorrhages were commonly situated in the positions of the arcuate nerve fibre bundles. The haemorrhages were usually fleeting, lasting from a few days to several weeks. As absorption proceeded, fragmentation of the haemorrhage could be observed, and in one case this was followed by local atrophy of the neuroretinal rim. No local

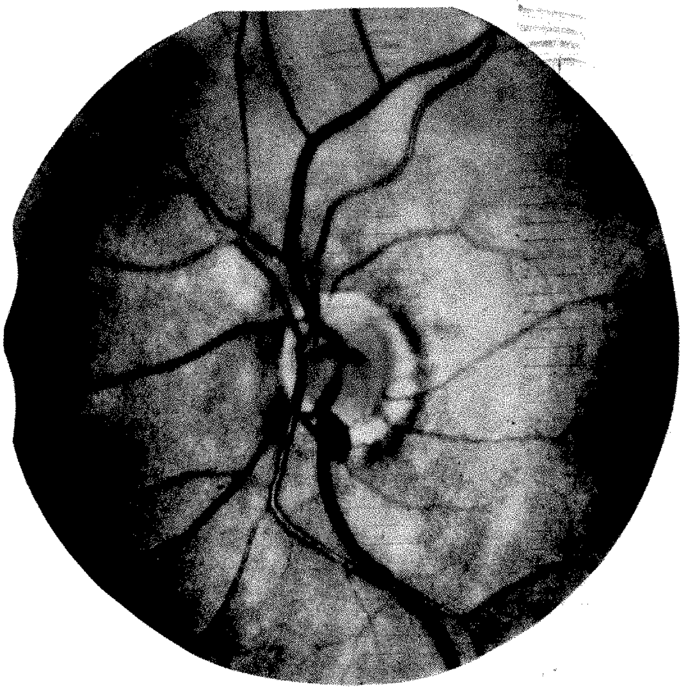

FIG. 18 *Case 2. Leading to fresh paracentral scotoma (shown in Fig. 5) Haemorrhage on inferior portion of disc*

swelling accompanied the haemorrhage except in one case in which the appearance resembled a local swelling of nerve fibres but not a soft exudate. No microaneurysms were seen and there were no signs of emboli or sheathing in any of the retinal vessels.

PROGRESSION OF FIELD DEFECTS

The appearance of the disc haemorrhage was accompanied by a step-like progression of field defects. These abrupt changes were associated with, but not produced by, a linear haemorrhage on the disc. In all seven cases, the field defect corresponded to the arcuate nerve fibre bundles at the neuroretinal rim in the position of the haemorrhage. In some of the other cases in our series of thirty patients no field defect could be plotted to correspond to the disc haemorrhage, but the possibility remained that the nerve fibre bundle defect was too small to detect even by the present techniques. The onset and progression of visual field defects resembled the sequence described by Aulhorn and Harms (1966). The following fresh defects were observed:

(1) An absolute paracentral scotoma close to fixation.
(2) An absolute paracentral scotoma in the Bjerrum area adjacent to the horizontal meridian.
(3) An absolute scotoma adjacent to the horizontal meridian between the 30° and 65° isopters.
(4) An absolute nucleus in a previously relative paracentral scotoma.
(5) The extension of an absolute arcuate-shaped paracentral scotoma.
(6) The appearance of a completely new absolute arcuate scotoma.

Discussion

Glaucomatous atrophy of the nerve head is characterized by a general reduction in the capillary circulation (Elschnig, 1928; Cristini, 1951; François and Neetens, 1966; Hayreh and Walker, 1967; Oosterhuis and Gortzak-Moorstein, 1970; Hayreh, 1969). A reduction in the number of capillaries, particularly severe in the laminary region, as well as obliteration of the choriocapillaris and peripapillary choroidal atrophy, has been reported pathologically (Cristini, 1951). These choroidal vessels are the main source of blood supply to the prelaminar plexus (Hayreh, 1969; Henkind, Charles, and Pearson, 1970), and are not only subject to degenerative changes in chronic open-angle glaucoma but are also the most vulnerable portion of the choroidal circulation when the intraocular pressure is acutely raised in animals (Hayreh and Perkins, 1969; Ernest and Potts, 1968) and man (Blumenthal, Gitter, Best, and Galin, 1970). Clinically, notching of the neuroretinal rim, especially in the areas corresponding to the arcuate nerve fibres, is a feature of glaucomatous cupping (Kronfeld, 1968).

In a previous communication (Drance and Begg, 1970) it was suggested that the haemorrhage on the neuroretinal rim of the optic disc and the fresh field defect in these glaucomatous cases was the result of a segmental ischaemic optic neuropathy occurring as a result of small vessel disease, perhaps at a capillary level. This assumption can be supported by the symptomless, discrete nature of the papillary haemorrhage and field defect characterizing damage to the arcuate nerve fibre bundles in marked contrast to the symptoms and signs of total and subtotal infarction of the optic nerve head (Miller and Smith, 1966; Ellenberger and Netsky, 1968). When infarction is subtotal patients almost always present with central visual failure or severe nerve fibre bundle damage often producing altitudinal hemianopia. Arcuate scotoma (Miller and Smith, 1966; Hoyt, 1962; Enoksson, 1965; François, Verriest, Neetens, de Rouck, and Hanssens, 1962) and central scotoma (Foulds, 1969) have been reported. Pale oedema of the nerve head is usually, but not necessarily, present; it was not observed in the present series, perhaps on account of its symptomless or transient nature when associated with a discrete infarction. Segmental infarction followed by atrophy has been reported in ischaemic optic neuropathy (Enoksson, 1965), and following an embolic occlusion on the optic disc (Harrington, 1964b), or as a probable embolic occlusion of a posterior ciliary artery (Hoyt, 1962). Observation of some of the patients in this series has shown that the sectoral haemorrhage was eventually followed by circumscribed notching of the neuroretinal rim resulting in localized enlargement of the cup and the appearance of atrophy.

We could find no mention in the literature of symptomless arcuate scotoma caused by acute ischaemic changes at the optic disc in eyes with ocular hypertension. Haemorrhage on a sector of the disc accompanied by a corresponding fresh nerve fibre bundle defect was shown in three of the cases described, indicating the transition of ocular hypertension to chronic simple glaucoma.

In a pathological study of optic nerves from twenty cadavers, Ellenberger and Netsky (1968) found that the arterial supply of the optic nerve is subject to atherosclerosis and arteriosclerosis no less than other vessels of similar size. These degenerative vascular changes have been regarded as important aetiological factors in total and subtotal infarction of the optic nerve head (Miller and Smith, 1966; Ellenberger and Netsky, 1968; François and others, 1962; Foulds, 1969). In these reports, hypertension and cardiac disease was common, and diabetes was an occasional finding. Arteriograms that have been carried out in patients with ischaemic optic neuropathy have been normal, including filling of the ophthalmic artery (David, 1967). This clinical entity comes to attention because of visual symptoms, pale oedema of the disc, usually multiple flame-shaped haemorrhages, and usually severe nerve fibre bundle damage. The ischaemic optic neuropathy which we report is symptomless, small, and discrete. Oedema has not been seen, either because of the very small area involved or because it was only very transient.

A vascular, neurological, and laboratory assessment of the patients showed no evidence of circulatory decompensation or vasculitis, but there were signs of extraocular small vessel disease. In the present series, small vessel disease was associated either with ischaemic heart disease or hypertension, or a positive glucose tolerance test, or a combination of these factors. A hypercoagulable state may be another contributory factor. The only patient without significant vascular disease had a family history of glaucoma and a very low blood pressure.

Some of the known deleterious and favourable factors which seem to influence perfusion of the optic nerve head have been briefly mentioned in a previous report (Drance and Begg, 1970). Patients with marked glaucoma-like damage to the optic nerve head and advanced visual field loss, with or without elevated intraocular pressure, have been shown, in retrospective studies, to have a low "diastolic perfusion pressure" as measured by ophthalmodynamography (Johnson and Drance, 1968) or a history of an acute haemodynamic crisis. Patients showing progressive field change were thought to have a low "efficient gradient" as measured by ophthalmodynamometry (Lobstein, 1968). In our group of patients, at the time when the disc haemorrhage and field loss were observed, the intraocular pressure, under treatment, was either within normal limits or only slightly elevated. Using the ophthalmodynamometric technique of Weigelin and Lobstein (Weigelin and Lobstein, 1963), no deficit between expected and obtained diastolic and mean ophthalmic artery pressures was present, nor was there any significant dynamometric difference between the two sides. Using the concept of "efficient gradient" (Lobstein, 1968), this did not suggest an impaired perfusion pressure except in one patient with a very low blood pressure; this suggests that the ischaemic optic neuropathy was probably related to small vessel disease, a theory which is supported by the frequency of extraocular small vessel disease found on general assessment of many of these patients.

Summary

The occurrence of discrete, recurrent, and sometimes bilateral haemorrhages in sectors of the disc, in the region of the arcuate nerve fibres, associated with fresh absolute field defects in the Bjerrum area was thought to characterize symptomless ischaemic optic neuropathy. These changes were observed in three patients with ocular hypertension, marking the transition to chronic simple glaucoma. A similar sequence marked the progression of field loss in four patients with chronic simple glaucoma. The general and neurovascular assessment of the patients, their level of intraocular pressure at the time of the field loss, and the ophthalmodynamometric findings suggested that the ischaemic optic neuropathy in this group of patients was probably due to small vessel disease, producing inadequate perfusion of the optic nerve head. Adverse perfusion pressures were seen in only some of this group of patients, which suggests that there are many causes for poor perfusion at the optic nerve head. An imbalance between intraocular pressure and vascular pressure, while common, is not the only cause of a nerve fibre bundle infarction indistinguishable from that found in chronic simple glaucoma.

We wish to express our thanks to Dr. W. R. Morton for letting us study some of his patients and to Mrs. M. Fairclough and Miss J. Bryett for the excellence of the fields.

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Studies on experimental retinitis

Light and electron microscopy

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Machemer (1968) and Kroll and Machemer (1969a, b) studied the ultrastructure of mechanically detached retinae in owl and rhesus monkeys. They found that in detached retinae the outer segments of the rods and cones became disorganized; when the retinae were reattached, however, the saccules of the outer segments were regenerated by the inner segments and the retinae resumed their normal architecture.

Our interest has been in the pathology of retinitis and the ensuing irreversible changes in the detached retina. Ocular siderosis creates intraocular inflammation which primarily affects the retina (Cibis and Yamashita, 1959; Hogan and Zimmerman, 1962). By injecting soluble iron into the vitreous of rabbits we produced a severe retinitis which was studied by light and electron microscopy. The purpose of this paper is to report the ultrastructural changes that occurred in the retina during and after experimental inflammation.

Material and methods

Saccharated iron oxide* or iron-dextran complex** was injected directly into the vitreous of albino or pigmented rabbits. Various doses were used: 0·5, 1, 1·5, and 3 minims. A half-inch 27 gauge hypodermic needle was inserted into the vitreous through the sclera and pars plana about 5 mm. behind the temporal limbus, slanting the needle slightly posteriorly in order to avoid the lens. Only one injection was given, always into the right eye; the left eye remained untreated as a control. Other control eyes were taken from animals that had received no treatment of any kind. The animals were killed at intervals of 1, 6, 12, 18, and 24 hours; at 1, 2, and 6 weeks; and at 4 and 6 months.

For light microscopy, the eyes were fixed in neutral formalin, embedded in paraffin, and sections stained with haematoxylin and eosin, Prussian blue, and the Quinche method for demonstrating iron (Lillie, 1965).

For electron microscopy, retinal samples were taken from calottes, fixed in buffered 1 per cent. osmium tetroxide for 1½ hours, dehydrated in graded alcohols, and embedded in Maraglas. Sections were cut on a Porter-Blum microtome, stained with lead citrate, and examined and photographed in a RCA EMU 3F microscope.

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Results

LIGHT MICROSCOPY

Intraocular injections of the iron-polysaccharide complex caused the following temporal sequence of changes in the retina. The earliest change noted by light microscopy was iron staining of the inner limiting membrane. Then came diffuse iron-positive staining suggesting diffusion of iron into the retina. Localization of iron-positive particles was next observed in the photoreceptor cells, and then the Müller fibres became swollen and later hyalinized and fragmented (Fig. 1). An acute inflammation followed with masses of leucocytes and monocytes in the vitreous. An inflammatory infiltrate also appeared in the choroid, and, when Bruch's membrane fragmented, the cells passed into the retina.

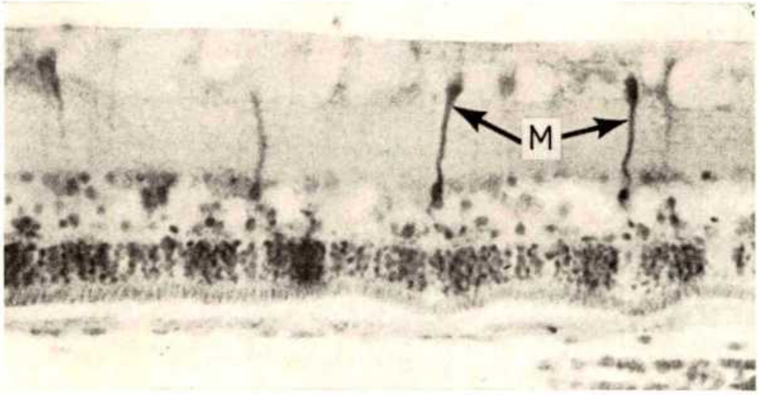

FIG. 1 *Rabbit retina 48 hrs after 0·5 minim intraocular injection of saccharated iron oxide. Hyalinized Müller fibres are beginning to fragment (M). Haematoxylin and eosin.* ×200

A 3-minim intraocular injection caused a more intense inflammatory reaction. Numerous eosinophils and monocytes were present in the vitreous, uvea, and retina by 18 hours. The inner and outer limiting membranes fragmented by 24 hours and inflammatory cells passed freely to the retina from both the vitreous and choroid.

Degeneration of the photoreceptor cell nuclei and the rod segments followed and the debris was phagocytized by macrophages. At 3 to 6 months after injection the retina was an atrophic membrane with areas of gliosis and detachment (Figs 2 and 3).

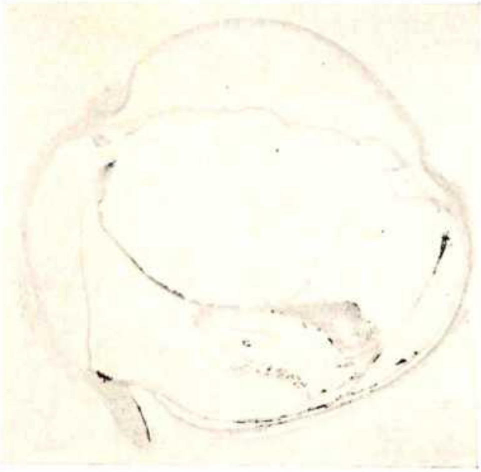

FIG. 2 *Albino rabbit eye 6 months after 1-minim intraocular injection of iron-dextran complex. The vitreous in the lower half of the eye still contains clumps of degenerating macrophages filled with iron. The retina consists of atrophic strands and iron is present on the optic disc and in the sheaths of the nerve. Prussian blue.* ×7

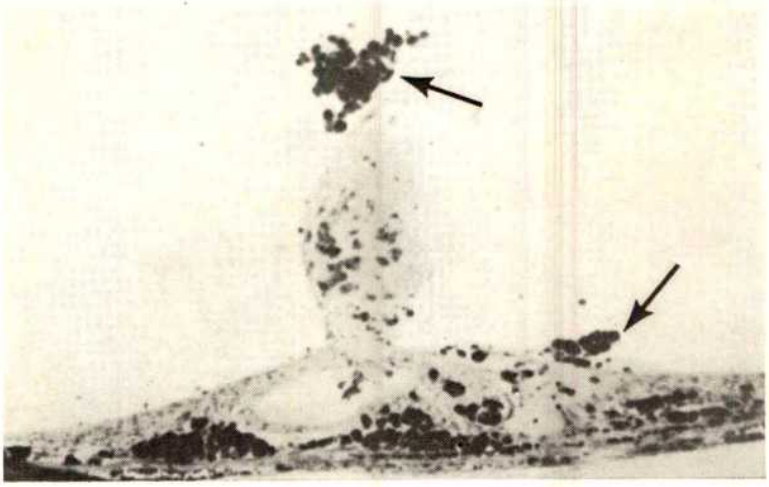

FIG. 3 *High-power view of the retina in the eye shown in Fig. 2. Dense fibres and a few glial cells remain. Prussian blue.* ×200

ELECTRON MICROSCOPY

Details of the electron microscopic examination, with controls shown in Figs 4, 5, 6, and 7 for comparison, are described more fully in the legends accompanying the illustrations. However, in general they confirm and elucidate the results seen by light microscopy.

Fig. 8 shows retinal detachment during the early stages of chorioretinal inflammation. (Compare with control shown in Fig. 4.) Many of the rod segments are fragmented and cellular debris has been scavenged by macrophages which have invaded the subretinal space. A portion of a rod outer segment can be seen in the sytoplasm of a macrophage (arrow). Fig. 9 shows a comparable stage in an albino rabbit. In this instance many fragments of rod outer segments are present in vacuoles deep in the cytoplasm of the pigment epithelial cells (arrows), and there is a relative increase in the number of mitochondria.

Marked degeneration of the nuclear layers followed. In Fig. 10 the nuclei of the rods are irregular in shape and vacuolated, and concretions of nuclear material are scattered throughout the cytoplasm. Numerous breaks are present in the outer limiting membrane (arrows). (Compare with control shown in Fig. 5.)

Fig. 11 shows a slightly later stage. The rod nuclei and inner and outer segments have disappeared, leaving the brush borders of the Müller fibres facing the subretinal space. An interesting feature at this stage is the presence of dilated cisternae in the granular endoplasmic reticulum. Macrophages, swollen with particulate matter, are also a prominent feature.

Large areas of retinoschisis developed by the 5th day. Cystoid spaces appeared in either the inner or outer plexiform layer, coalesced, and formed long splits in the retina. Three cystoid spaces are seen in the electron micrograph shown in Fig. 12. They involve mainly Müller fibres and are separated by nerve fibres in the inner plexiform layer. This illustration should be compared with controls shown in Figs 6 and 7. Comparison with the photomicrograph shown in Fig. 1 suggests that fragmentation of Müller fibres seen by light microscopy may explain the appearance of the cystoid spaces. The inner ends of the Müller fibres are also swollen and show an increase in the amount of agranular endoplasmic reticulum which corresponds to the swollen appearance of the fibres in Fig. 1.

Electron microscopy was particularly revealing in the study of the healing process in experimental retinitis. After degeneration and removal of the cellular elements of the retina and

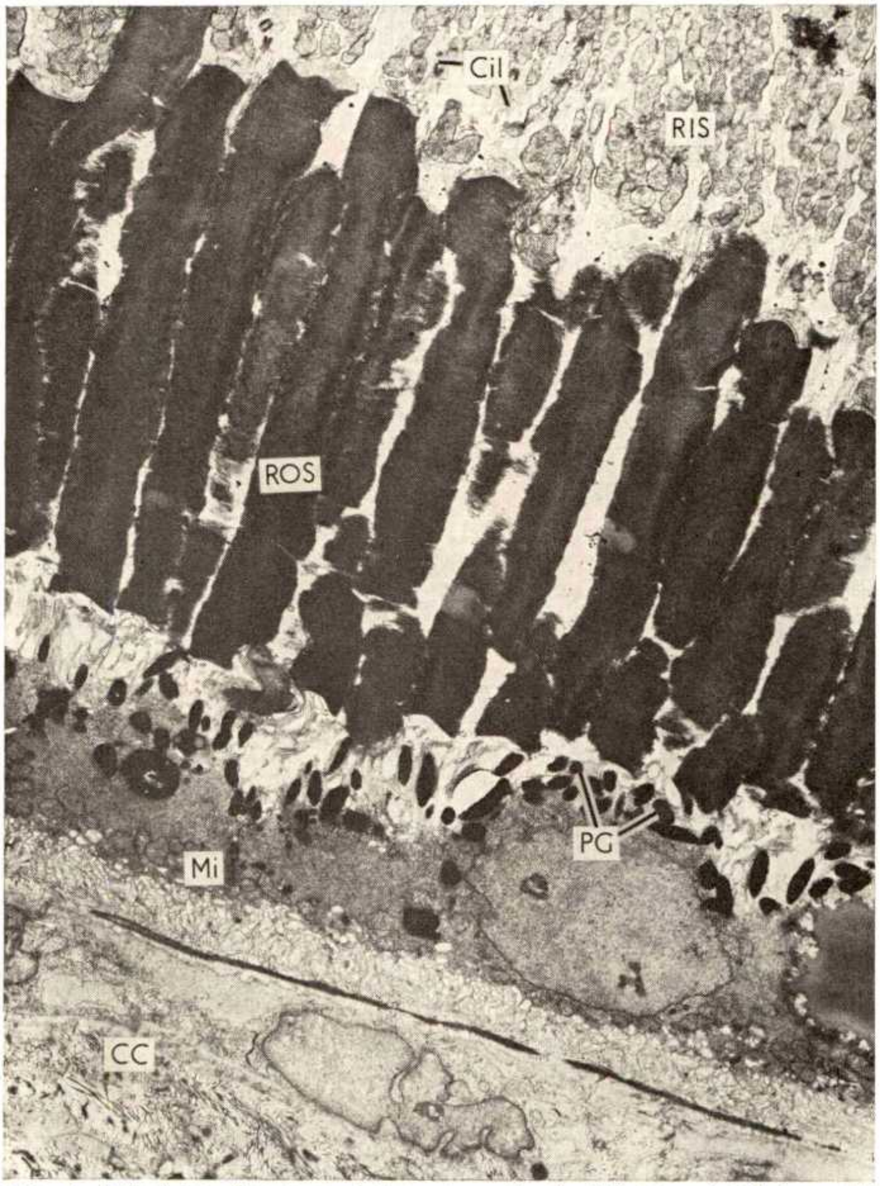

FIG. 4 *Control eye. Low-power electron micrograph of rabbit pigment epithelium. The external third of the epithelial cells is composed of a deep complex of basal infoldings of the cell membrane which lies adjacent to an inner layer of mitochondria (Mi). The inner third of the cells contains large disc or irregularly-shaped pigment granules (PG). Many of the granules occupy the ends of microvilli which cover the inner surface of the cells and penetrate between the rod outer segments. Several connecting cilia can be seen between the inner and outer segments.* ×5,000
RIS, rod inner segment; ROS, rod outer segment; Cil, connecting cilium; CC, choriocapillaris. ×5,000

the inner and outer segments of the rods, the remaining Müller fibres were united to each other by the formation of desmosomes. Attachment zones were also formed between outer ends of the Müller fibres and the pigment epithelium (Figs 13, 14, and 15). (Compare with controls shown in Figs 4 and 5.) In Figs 13 and 14a the brush borders are still present on the ends of a few Müller fibres, but have disappeared in the region of reattach-

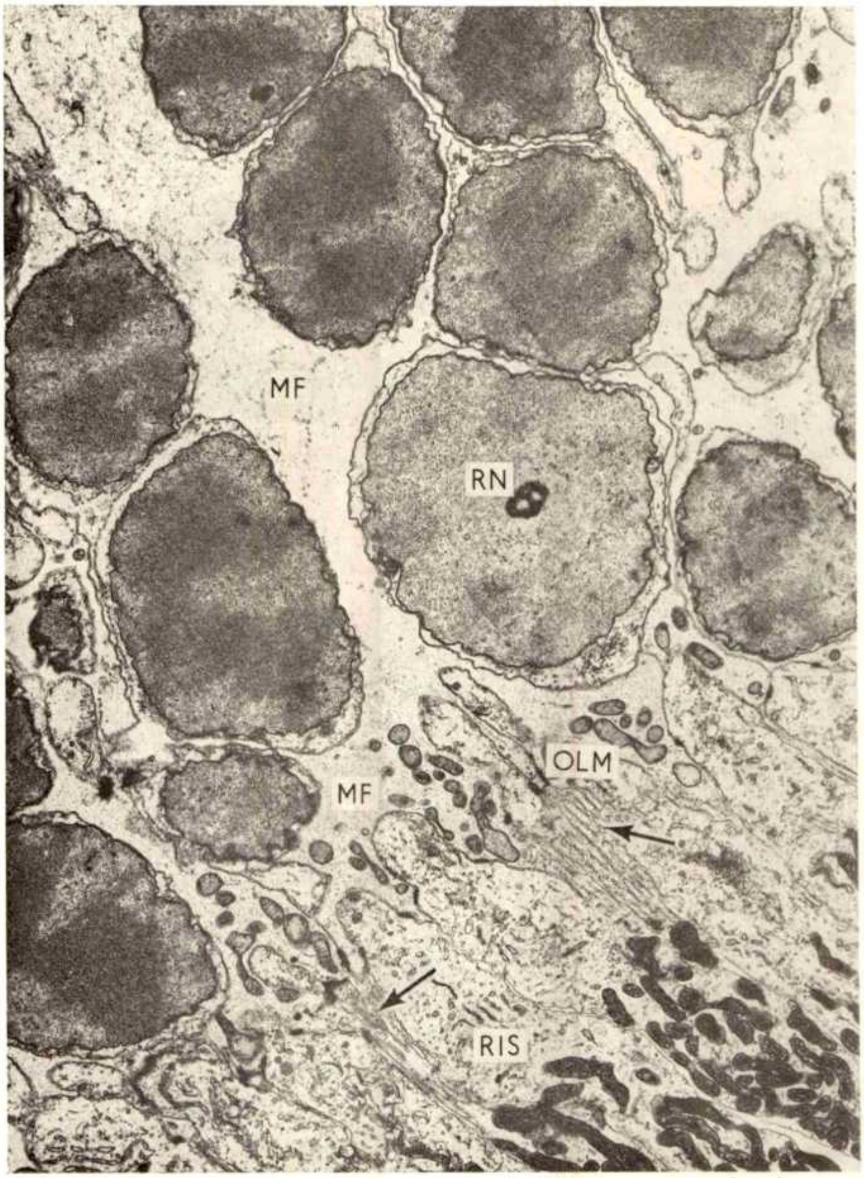

FIG. 5 *Control eye. Low-power electron micrograph which shows outer nucleus layer, and external limiting membrane (OLM) composed of desmosomes (zonular adherens) which attach the Müller fibres (MF) to the rod inner segments (RIS). The brush borders of the Müller cells are indicated by arrows.*

RN, rod nuclei. × 5,000

ment (arrows). During the healing process the epithelial cells were very active, proliferated, and formed mounds several cells deep; some became distended by large vacuoles as seen in Fig. 14b.

The desmosomes which united the Müller fibres with the epithelial cells were very strong. Fig. 15 shows an area where the epithelium was accidently torn from Bruch's membrane, yet it remained with the Müller cells even though the attachment zones were of recent formation.

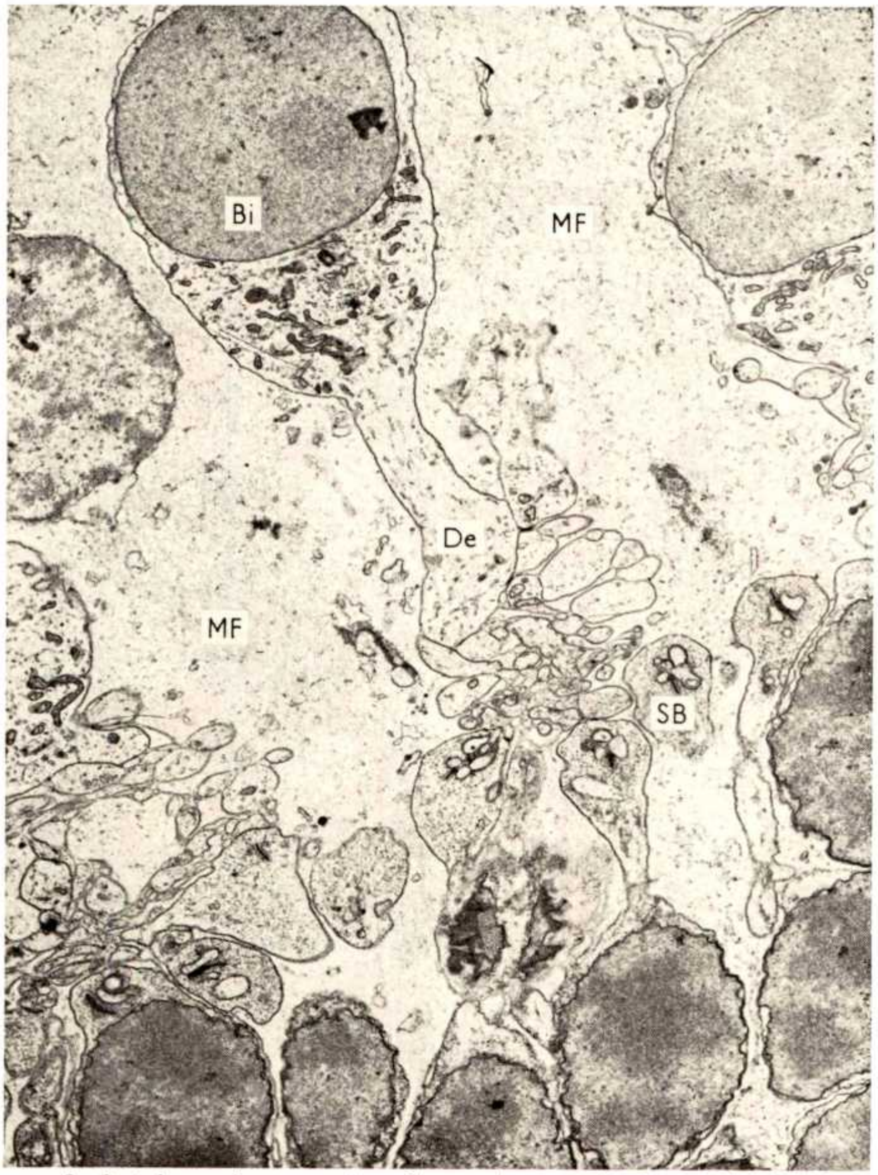

FIG. 6 *Control eye. Low-power view of inner and outer nuclear layers and outer plexiform layer of rabbit retina. Several bipolar cells (Bi) are present in the inner nuclear layer and their dendrites (De) extend into the outer plexiform layer. Numerous synaptic bodies (SB) with synaptic vesicles are present in the rod axones. Müller fibres (MF) fill the extracellular spaces between the outer cellular elements.* × 7,000

Comment

The main contribution of this study is the demonstration of the ultrastructure of degenerative changes during inflammation of the retina and the resolution of these changes. In contrast to reattachment of the retina after mechanical detachment studied by Kroll and Machemer (1969 a, b), the reattachment after retinal inflammation occurs as a result of the formation of new connections (desmosomes) between cells that were not originally attached; that is, the Müller fibres and the pigment epithelial cells.

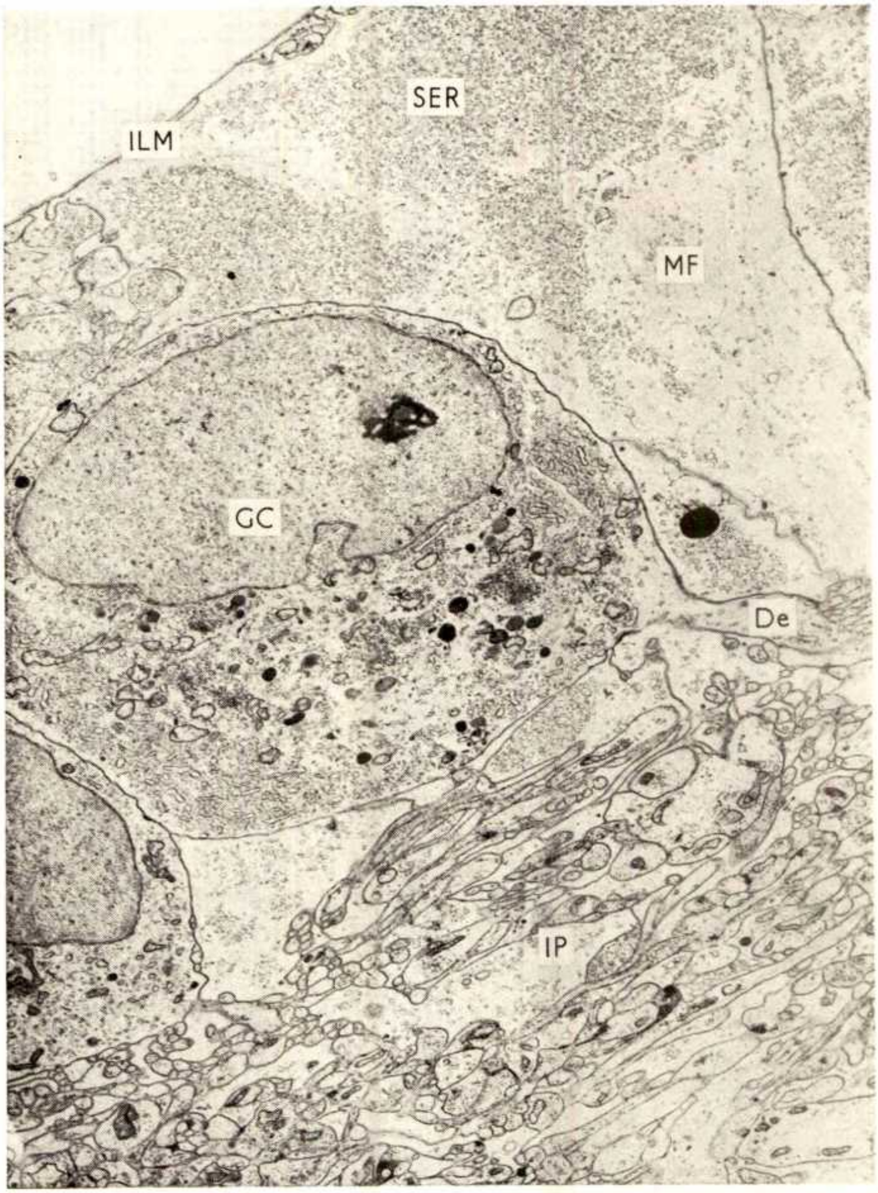

FIG. 7 *Control eye. Electron micrograph of the inner portion of rabbit retina. A ganglion cell (GC) with dendrite (De) entering the inner plexiform layer (IP) is seen in the centre. Müller fibres (MF) fill the extracellular space and their expanded ends form the internal limiting membrane (ILM). Agranular endoplasmic reticulum (SER) is a prominent feature of the inner ends of the Müller fibres.* ×7,000

The reorganization of a new outer limiting membrane by formation of desmosomes between the viable Müller fibres that remain in the atrophic retina is also an interesting feature of the healing process. These attachment zones reunite the elements of the retina into an atrophic, but intact membrane.

Many of the degenerative changes seen in our material were described by Shakib and Ashton (1966) in their comprehensive study of the ultrastructural changes in the retina following ischaemia. The swelling of the nuclei and their final rupture, concretions of

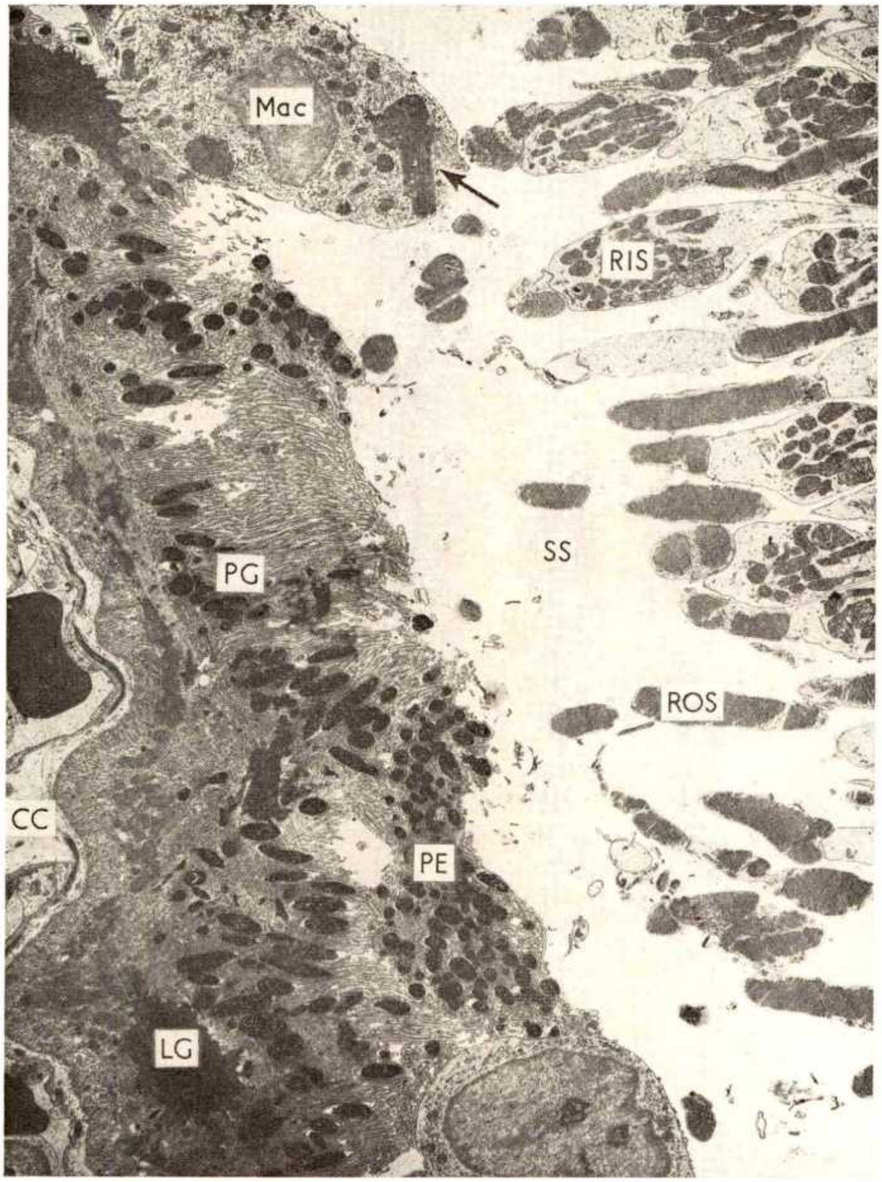

FIG. 8 *3-minim intraocular injection of iron-dextran complex after 14 days. This low-power electron micrograph shows a lesion where the retina is detached. Many rod outer segments have been destroyed. Macrophages (Mac) have entered the subretinal space and ingested cellular debris. A fragment of a rod outer segment (ROS) is present in the cytoplasm of a macrophage (arrow). Some of the pigment granules (PG) have withdrawn to the interior of the epithelial cells but many remain at the tips of the macrovilli. In the centre a pigment epithelial cell (PE) is detached from the epithelium.*

LG, lipid globule; CC, choriocapillaris; SS, subretinal space. × 4,000

nuclear material in the cytoplasm, and dilatation of the cisternae of the granular endoplasmic reticulum found in our material agree with their observations.

We would not confirm their observations on the origin and fate of the phagocytic cells in the pig, since the rabbit retina is free of blood vessels except on the inner surface near

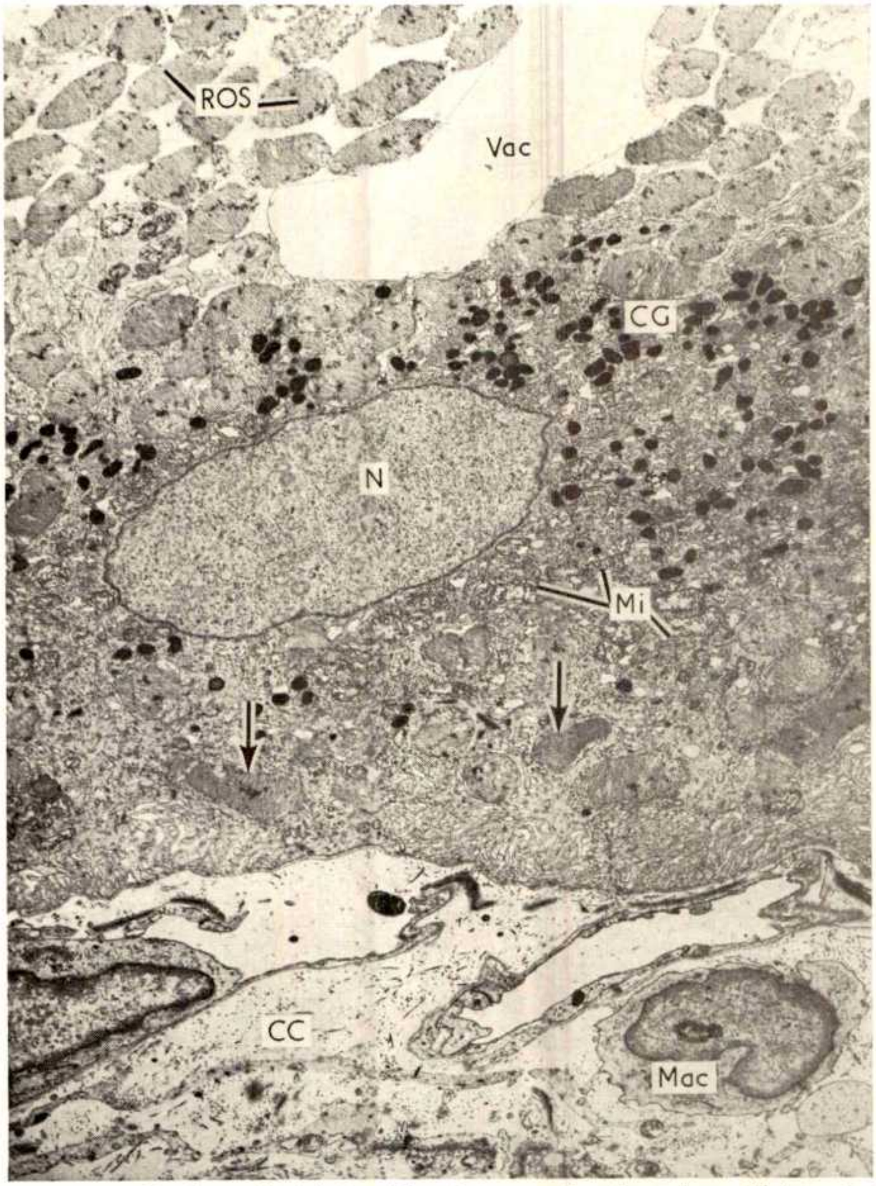

FIG. 9 *1-minim intraocular injection of iron-dextran complex after 5 days. Electron micrograph of retinal epithelium of an albino rabbit. Microvilli on the apical surface of epithelial cells surround fragments of rod outer segments (ROS). Many of the fragments are within vacuoles deep in the cytoplasm (arrows), and there is a relative increase in mitochondria. Numerous cytoplasmic globules (CG) are also scattered throughout the cytoplasm.*

N, nucleus; Mi, mitochondria; Vac, vacuole; CC, choriocapillaris; Mac, macrophage. ×5,400

the optic disc. Most of the macrophages seen by us arrived from outside the retina at least during the early stages of inflammation. They appeared first in the vitreous and were mainly eosinophils with a few monocytes. Almost immediately afterwards they were found in the stroma and blood vessels of the choroid. As soon as breaks developed in the inner limiting membrane, the macrophages entered the retina. A larger

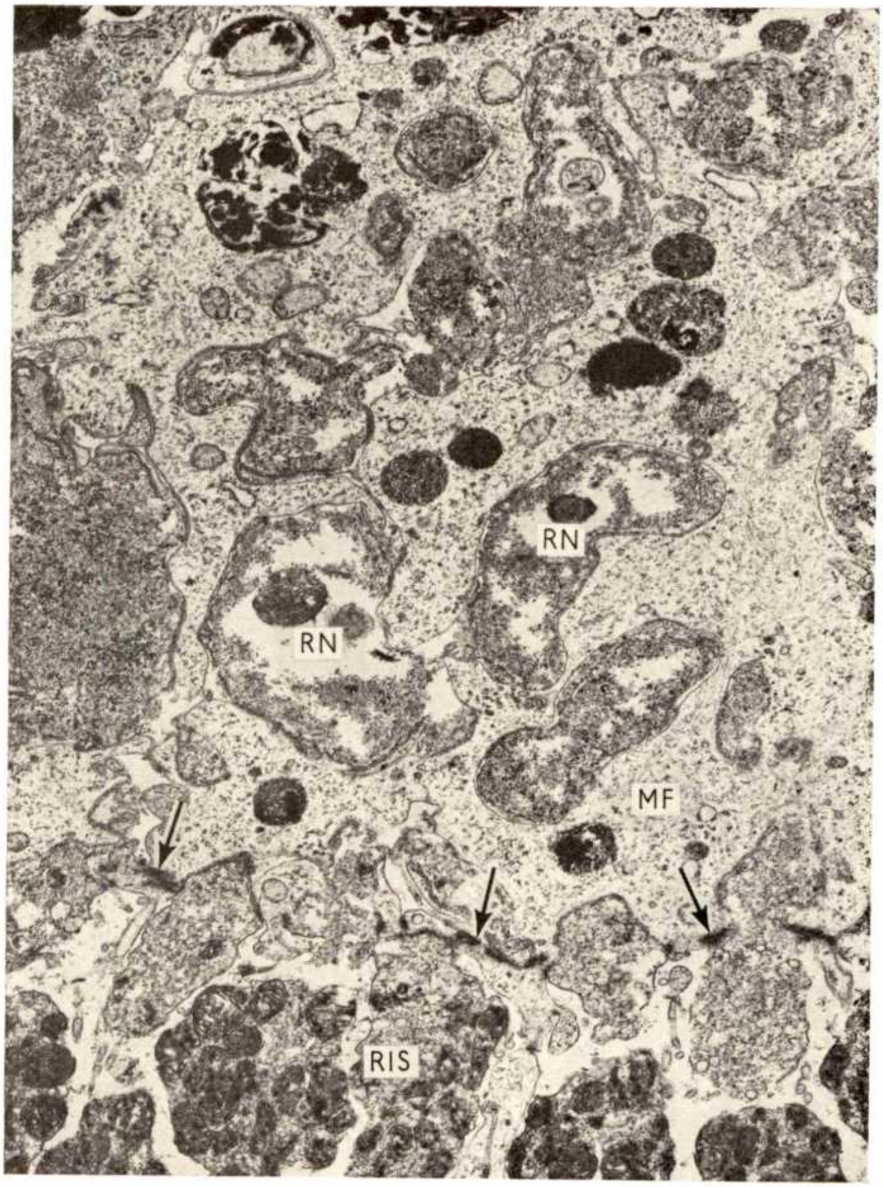

FIG. 10 *1-minim intraocular injection of iron-dextran complex after 3 days. Electron micrograph, showing rabbit retina. Marked degeneration of the rod nuclei (RN) has occurred and the external limiting membrane (arrows) is disorganized.*

MF, Müller fibres; RIS, rod inner segment. (Compare with Fig. 6) × 11,250

number, however, entered the subretinal spaces through breaks in Bruch's membrane, and migrated thence to the retina. By the time the macrophages could be identified in the retina, their origin could not be differentiated as was possible in the work of Shakib and Ashton (1966).

It is interesting to speculate about the healing process in experimentally-produced retinitis and the condition known as "healed chorioretinitis" in humans. Electron microscopic studies on primates are in progress in this laboratory to determine whether

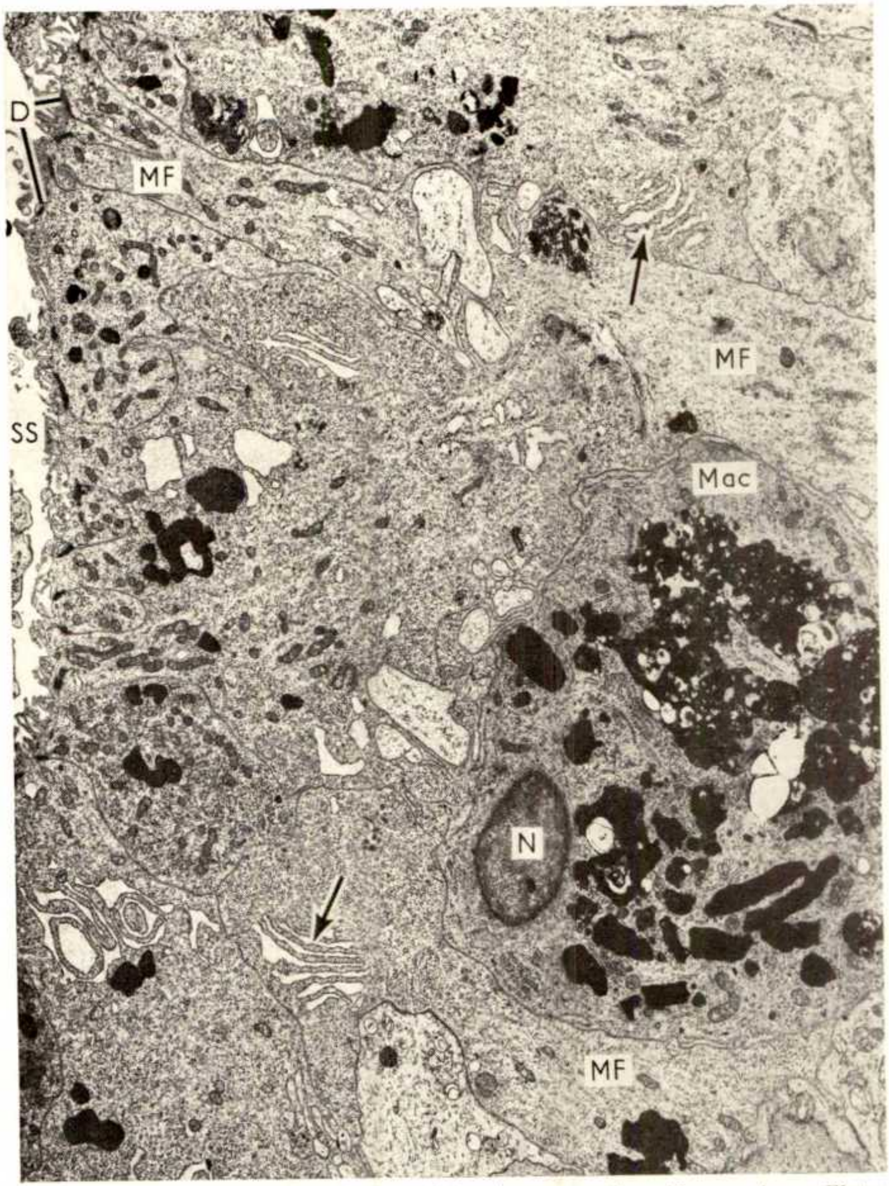

FIG. 11 1-*minim intraocular injection of iron-dextran complex after* 14 *days. Electron micrograph of outer portion of rabbit retina shows absence of rods and their nuclei. A macrophage can be seen on the right. Dilated cisternae of the granular reticulum are indicated by arrows. Desmosomes* (*D*) *unite the Müller fibres* (*MF*) *and the brush borders of these fibres are short and reduced in number.*

Mac, macrophage; N, nucleus; SS, subretinal space. (Compare with Figs 2 and 3) × 5,250

or not the adhesions formed between the retina and choroid after chorioretinal inflammation are desmosomes.

Summary

Experimental retinitis, created by intraocular injections of an iron-polysaccharide complex, has been studied by means of light and electron microscopy. The electron microscopy

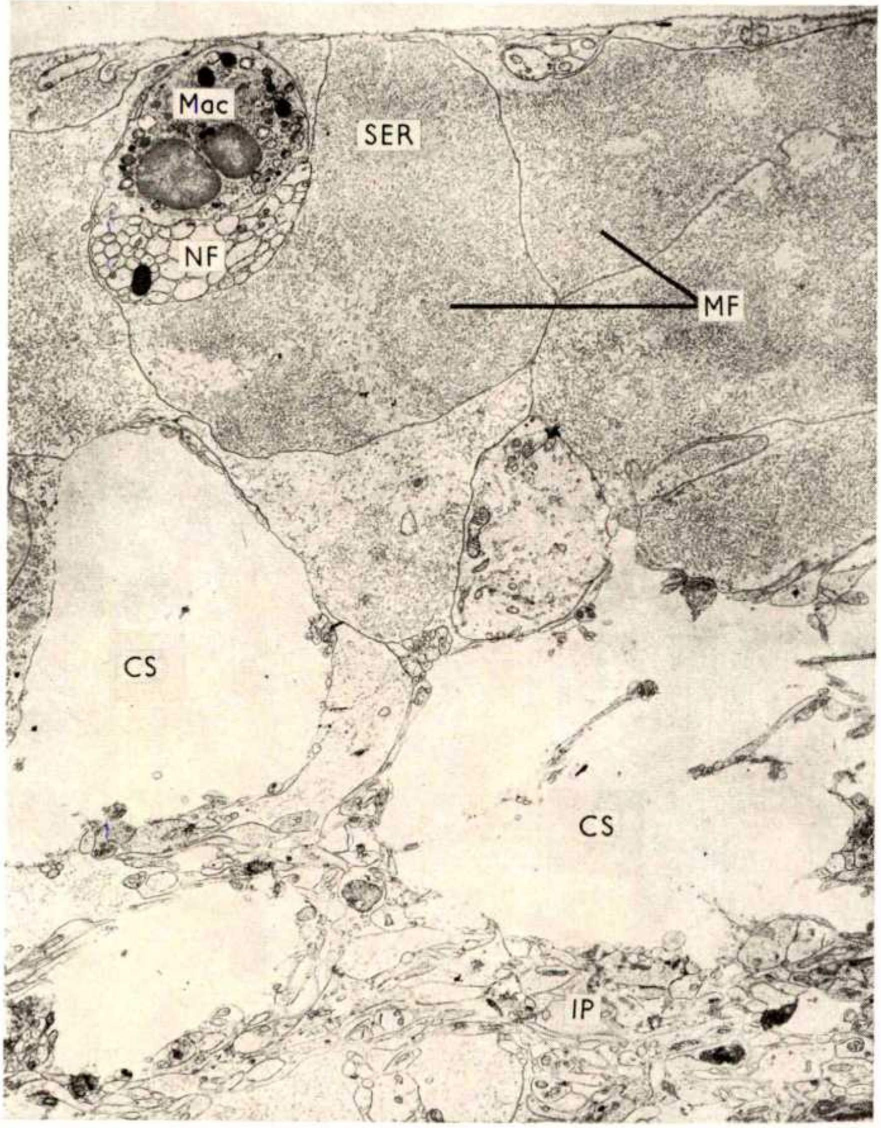

FIG. 12 *3-minim intraocular injection of iron-dextran complex after 24 hours. Low-power electron micrograph shows an increase in the amount of granular reticulum (SER) in the vitreal ends of the Müller fibres (MF) and cystoid spaces (CS) in the inner plexiform layer (IP). The cystoid spaces are in areas where the Müller fibres are missing. A macrophage (Mac) is seen at the left.*

NF, nerve fibres. (Compare with Fig. 7) × 4,200

confirmed the light microscopy and added new information, especially about the healing process.

The salient facts are:

(1) Early destruction of the photoreceptor cell nuclei and their segments;

(2) Retinoschisis or splitting of the inner or outer plexiform layers by fragmentation of Müller fibres;

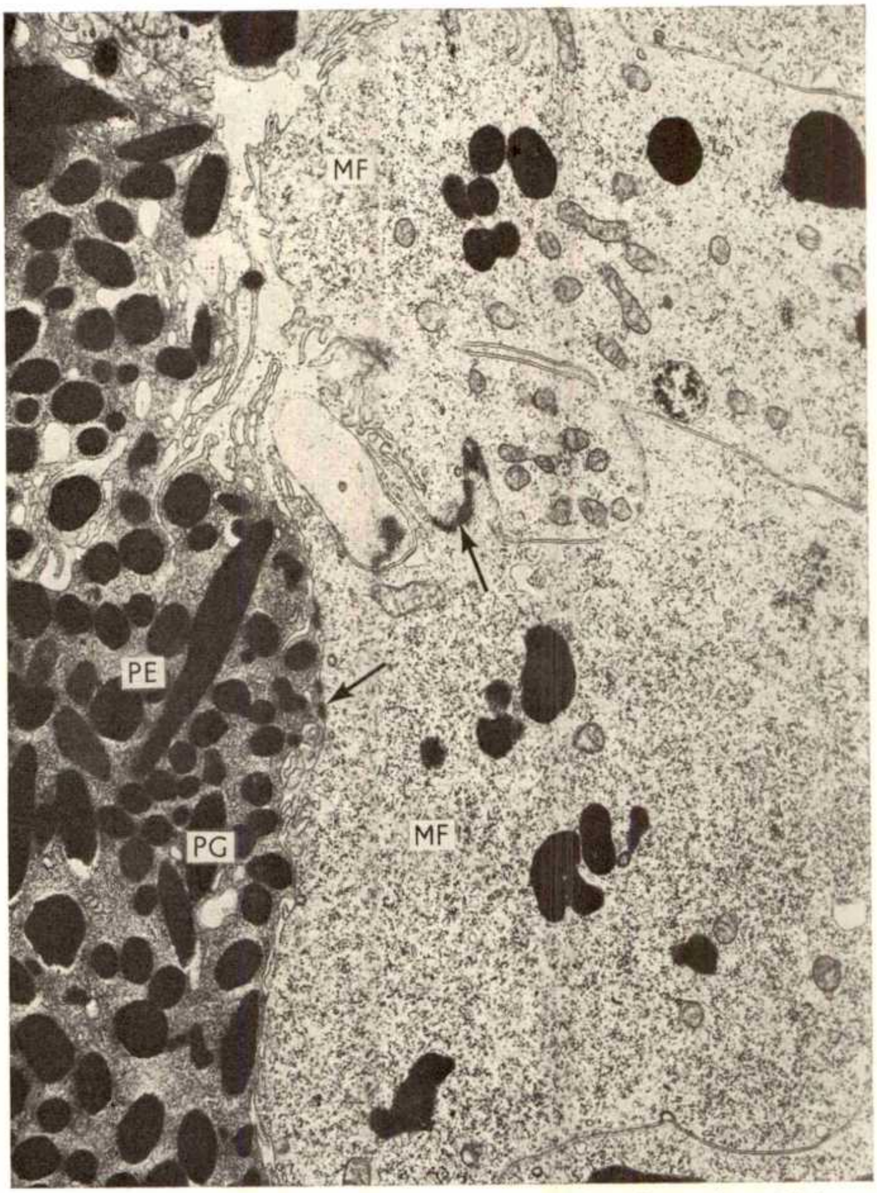

FIG. 13 *1-minim intraocular injection of iron-dextran complex after 14 days. High-power electron micrograph of retinal reattachment. The rod nuclei and segments have disappeared. Desmosomes (arrows) form an attachment zone uniting the outer ends of Müller fibres to each other, forming a new outer limiting membrane, and other desmosomes attach the fibres to the pigment epithelium, thus reattaching the atrophic retina to the epithelium. Notice the loss of the brush borders of the Müller fibres and retraction of the microvilli of the pigment epithelial cells.*

MF, Müller fibre; PE, pigment epithelium; PG, pigment granule. (Compare with Fig. 4) × 15,750

(3) Formation of a new outer limiting membrane by desmosomes which unite the Müller fibres;

(4) Sealing of the retina to the pigment epithelium by newly formed desmosomes without reversal of the destructive process.

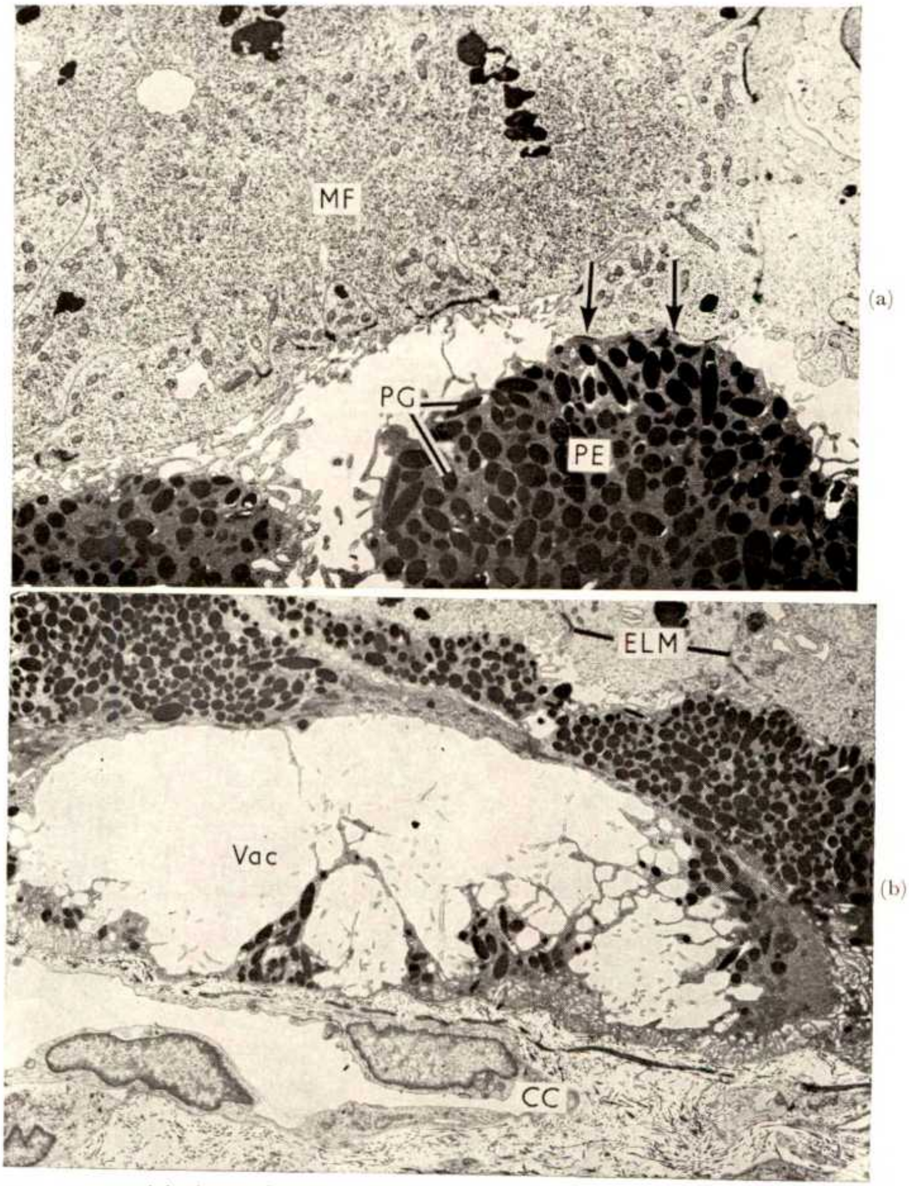

FIG. 14 *1-minim intraocular injection of iron-dextran complex after 14 days.*

(*a*) The pigment epithelium (PE) has proliferated and formed a mound of cells beneath the retina. Pigment granules (PG) are scattered throughout the cytoplasm and are absent from the microvilli. As the epithelial cells come in contact with Müller fibres (MF), the microvilli disappear and desmosomes (arrows) are formed. × 5,250

(*b*) From same eye as (*a*). Pigment epithelial cell with a large intracellular vacuole (Vac) which replaces almost the entire cell.

ELM, external limiting membrane; CC, choriocapillaris. × 3,750.

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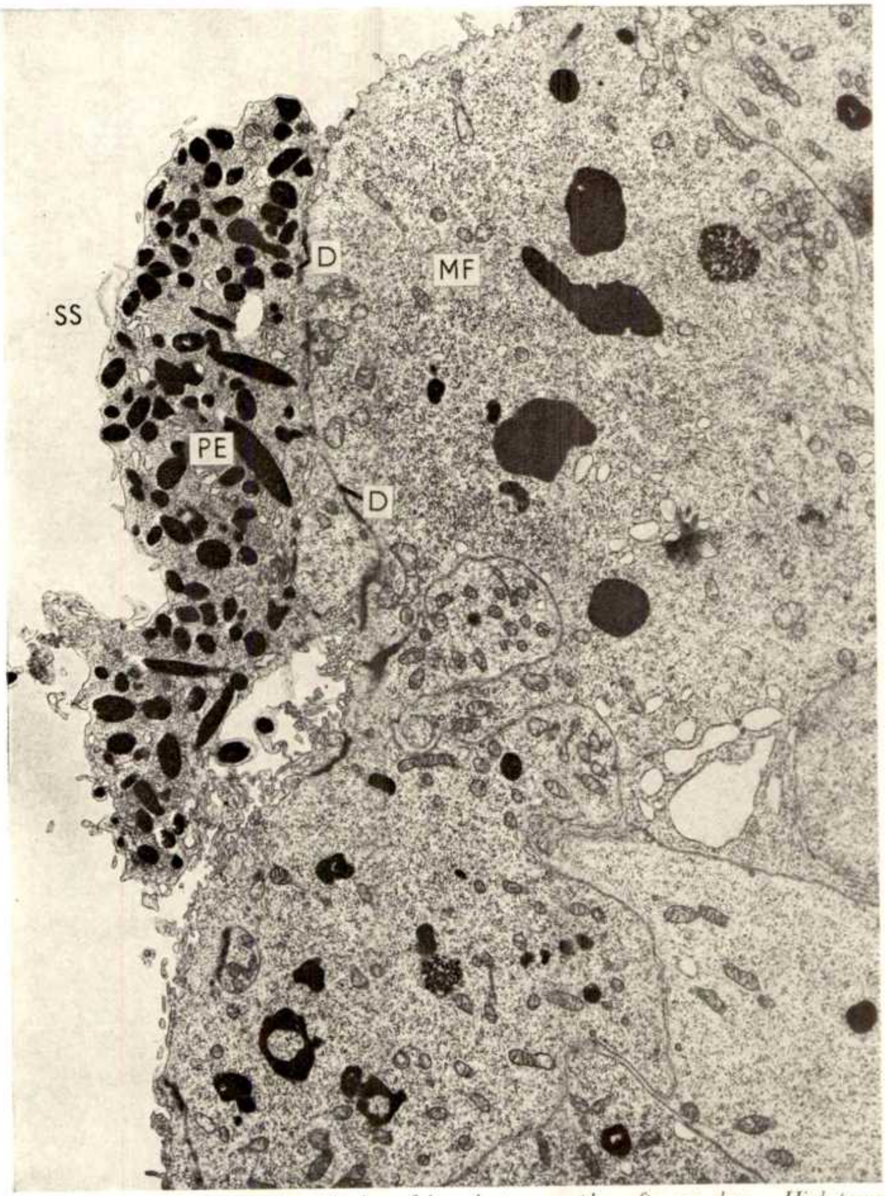

FIG. 15 *1-minim intraocular injection of iron-dextran complex after 14 days. High-power electron micrograph, showing strength of retinal reattachment. The pigment epithelium (PE) was accidentally torn from the choroid during preparation of this section, yet epithelial cells remained attached to the retina by the recently formed attachemnt zones (desmosomes) in spite of their original attachment to the choroid. Where the retina and epithelium are reattached, the brush borders of the Müller fibres (MF) and the microvilli of the epithelium have disappeared.*

SS, subretinal space; D, desmosome. × 8,000

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Experimental ocular schistosomiasis

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Schistosomiasis is a widespread incapacitating disease, but ocular involvement is relatively rare.

The first of the few cases of ocular schistosomiasis recorded in the literature was that reported in Egypt by Sobhy Bey (1928). Others were recorded by Wilson (1934), Barsoum (1938), Ibrahim (1941), Kamel (1948), Naim (1948), Mohamed (1956), and Sparrow (1966). All these took the form of bilharzial granuloma in the conjunctiva, which revealed the presence of *Schistosoma haematobium* ova. Adult *Schistosoma* worms were reported for the first time by Badir (1946) in a branch of the superior ophthalmic vein. Newton, Kanchanaranya, and Previte (1968) extracted a specimen of *Schistosoma mansoni* from the anterior chamber.

Other ocular lesions in cases of generalized schistosomiasis, which were claimed to have responded to antischistosomal treatment, were albuminuric retinitis (Ahmad, 1924); embolus in the inferior nasal branch of the central retinal artery (Cecchetto, 1931); keratitis, iritis, chorio-retinitis, vitreous opacities (de Andrade, 1940); mydriasis, palpebral oedema (Meira, Behmer, and Bloise, 1951); chronic conjunctivitis, corneal dystrophy, exophthalmos, chronic uveitis, tortuosity of the retinal veins, errors of refraction especially mild myopia (Machado, 1956); and pre-retinal haemorrhage (Massa, Laurijs, and Wijns, 1964).

Bilharzial granulomata in the conjunctiva may appear in the form of yellowish-pink nodules, either single or multiple, in the bulbar conjunctiva. In the palpebral conjunctiva, they may resemble chalazia, or may appear as polypoid cauliflower masses, resembling trachomatous pannus, arising from the fornices and extending up to the corneal margin. Scattered nodules at the caruncle may resemble *Streptothrix* nodules (Kamel, 1948; Attiah, 1962).

Histologically, the bilharzial granuloma consists of a subepithelial mass made up of endothelial cells, lymphocytes, plasma cells, eosinophils, and giant cells. *Schistosoma* ova are found in the centre in various stages of disintegration, and are frequently surrounded by giant cells (Duke-Elder, 1965).

In the early period of generalized invasion by *Schistosoma*, ocular manifestations in the form of urticaria and oedema of the lids may be seen (Sorsby, 1963). In the terminal phase of eastern schistosomiasis (kayayama disease), the involvement of the meninges and cerebral cortex may give rise to visual disturbances and blindness (Somerset, 1962; Sorsby, 1963).

In an attempt to solve the aetiological problem of ectopic schistosomal lesions, such as those recorded in the skin or the eye, various theories have been postulated on the different routes by which the *Schistosoma* ova, or even the adult worms, can reach the systemic circulation. These include a patent foramen ovale; local infection (Diamantis, 1932);

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migration of worms against the blood stream (Day, 1937; Black, 1945); dissemination *via* the vertebral venous system (Batson, 1940; Gama and Marques Sa, 1945; Faust, 1948), or *via* the pulmonary capillaries.

Present investigations

The aim of our experiments was to discover whether the local route of infection could cause ectopic schistosomal lesions, whether infection leading to generalized schistosomiasis could enter by way of the eye, or whether schistosomiasis could affect the ocular structures.

The penetration of the *cercariae* of *Schistosoma mansoni* into ocular structures (including the eyelids, conjunctiva, sclera, and cornea) was studied in hamsters and guinea-pigs both *in vivo* and *in vitro*, and also the effect of injecting *cercariae* subconjunctivally and into the anterior chamber.

Evidence of generalized schistosomiasis was sought in animals subjected to the instillation of *cercariae* on to the eyelids, on to the conjunctival sac, and subconjunctivally. The eyes of animals which had been injected with *cercariae* intraperitoneally were also examined.

Clinical cases of schistosomiasis (*Schistosoma haematobium*, *Schistosoma mansoni*, and infections mixed with other parasites) were examined for ocular lesions.

Methods

Animals

Twenty golden Syrian hamsters weighing 80 to 100 g. and 28 South American guinea-pigs weighing 320 to 350 g. were used. The *cercariae* of *Schistosoma mansoni* (Egyptian strain) were used in concentrations of 80, 150, and 250 ml. The anaesthetic used was Nembutal (60 mg./kg. body weight) intraperitoneally, and urethane was also used for some animals (1–2 g./kg. body weight).

Cercarial penetration was studied with the dissecting microscope, the slit lamp, and serial histological sections. The right eyes of the animals were used throughout the experiments, leaving the left eyes as controls.

The specimens removed from the animals, which included the various ocular structures, enucleated globes, and internal organs such as the liver and spleen, were all fixed in 10 per cent. formalin solution and embedded in paraffin. Serial histological 6 to 8 μ sections were stained with haematoxylin and eosin.

The scheme on which our study was based is set out in Tables I to V.

INSTILLATION IN VIVO (Table I)

The hair on the eyelids was carefully shaved before the instillation, without injuring the skin, to avoid obstructing the penetration of *cercariae*. The instillation on to the eyelids and conjunctival

Table I *Instillation of* cercariae in vivo

Animals	*Site of instillation*	*Concentration/ml.*	*Animals killed after*
(*a*) 3 Hamsters	Eyelids	80	5, 10, 15 min.
(*b*) 3 Hamsters 3 Guinea-pigs	Conjunctival sac	80	5, 10, 15 min.
(*c*) 5 Guinea-pigs	Cornea	80–250	½, 1, 2, 6, 24 hrs

sac was made at a rate of one drop every 5 minutes for 15 minutes. For corneal instillation, a glass tube equal to the corneal diameter was placed vertically over the limbus for 10 minutes to allow as many *cercariae* as possible to come into contact with the cornea.

INSTILLATION IN VITRO (Table II)

The suspension was placed on the isolated cornea after rupturing the basal membrane. An artificial corneal ulcer was induced with the slit lamp where the corneal epithelium was scraped by a von Graefe knife and the basal membrane was ruptured. This was to permit the observation of the penetration of *cercariae* into the substantia propria, once the barrier of the basal membrane had been removed. The same procedure was then repeated with the anterior segment of the globe to detect whether the *cercariae* could penetrate Descemet's membrane and reach the anterior chamber.

Table II *Instillation of* cercariae in vitro

Animals	*Part instilled*	*Concentration/ml.*	*Duration of instillation (hrs)*
(*a*) 2 Hamsters 2 Guinea-pigs	Enucleated globes	250	1
(*b*) 1 Hamster 1 Guinea-pig	Isolated specimens from lids, conjunctiva, sclera, trephined cornea	250	2
(*c*) 2 Guinea-pigs	Isolated cornea (after rupturing basal membrane)	250	3

INJECTION IN VIVO (Table III)

The *cercariae* were injected subconjunctivally and into the anterior chamber, and the same amount of aqueous was previously aspirated from the anterior chamber so as not to alter the ocular tension.

Table III *Injection of* cercariae in vivo

Animals	*Site of injection*	*Amount (ml.)*	*Concentration/ml.*	*Animals killed after*
(*a*) 3 Hamsters	Subconjunctival space	0·2	250	3, 4, 5 mths
3 Guinea-pigs	Subconjunctival space	0·4	250	4, 5, 6 mths
(*b*) 3 Guinea-pigs	Anterior chamber	0·1	250	30, 40, 50 days

DETECTION OF GENERALIZED SCHISTOSOMIASIS (Table IV)

The animals were kept for 45 days to allow time for adult *Schistosoma* worms to develop, and perfusion was then performed to collect the organisms from the liver and mesenteric vessels. The animals were killed by cervical dislocation, as the use of an anaesthetic causes the worms to shift into the liver. Before the perfusion heparin was injected intracardially (0·2 ml. of 5,000 units) to facilitate flushing.

DETECTION OF OCULAR LESIONS (Table V)

The eyes were inspected by repeated slit-lamp and fundus examinations, and also by histological sections.

Table IV *Detection of generalized schistosomiasis*

Animals	*Site of instillation or injection*	*Concentration/ml.*	*Period before perfusion (days)*
(*a*) 1 Hamster 1 Guinea-pig	Eyelids	250	45
(*b*) 2 Hamsters 2 Guinea-pigs	Conjunctival sac	250	45
(*c*) 1 Hamster 1 Guinea-pig	Subconjunctival space	250	45
(*d*) 2 Guinea-pigs	Anterior chamber	250	45

Table V *Detection of ocular lesions*

Animals	*Injection*	*Concentration/ml.*	*Animals killed after*
(*a*) 2 Hamsters	Intraperitoneal	250	2, 4 mths
(*b*) 2 Guinea-pigs	Intraperitoneal	250	3, 5 mths

Humans

The eyes of 150 patients suffering from schistosomiasis, including *S. haematobium*, *S. mansoni*, and combined infestation (haematobium + mansoni), and also from mixed parasites (*Ascaris* and *Ankylostoma*) were also examined for ocular lesions.

Results

Animals

SKIN AND CONJUNCTIVAL INSTILLATION

The *cercariae* penetrated the skin of the eyelids at an average rate of 4·6 min. *in vivo* and 5·5 min. *in vitro* (Fig. 1).

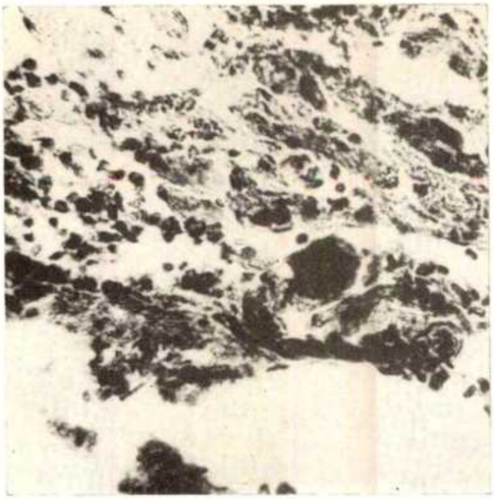

FIG. 1 *Cross-section of a* cercaria *after penetration of the eyelids of a hamster.* × 800

The average time for penetration of *cercariae* through the conjunctiva was 4·2 min. in hamsters and 4·4 min. in guinea-pigs *in vivo*, and 5·4 min. *in vitro* (Fig. 2).

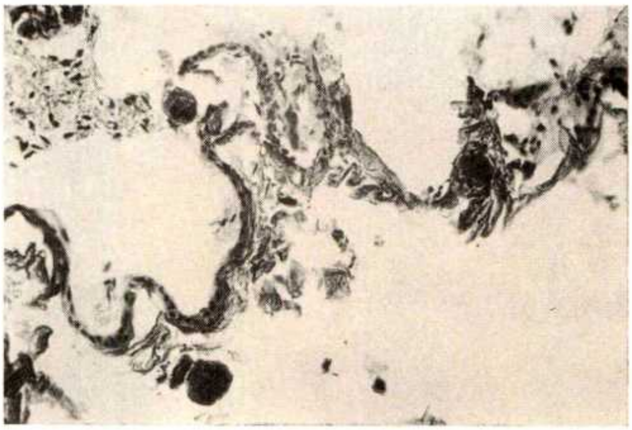

FIG. 2 *Cross-sections of three* cercariae, *showing penetration of one through the conjunctiva of a hamster.* × 800

Penetration occurred mostly at the fornices and medial and lateral canthi. In the bulbar conjunctiva of enucleated globes of guinea-pigs, the average time of penetration was 5·4 min., and in isolated bulbar conjunctiva it was 5·1 min. Neither the sclera nor the episclera was penetrated by the *cercariae*.

CORNEAL INSTILLATION

When *cercariae* were instilled on to the cornea of guinea-pigs, they penetrated the epithelial layer only. An average of 13·1 min. elapsed before the *cercariae* reached the basal membrane *in vivo*, and an average of 14·7 min. *in vitro*. Three stages of epithelial penetration were noticed:

(**1**) The *cercariae* were held to the corneal epithelium by their oral suckers, and penetrated the flattened epithelium in a perpendicular direction.

(**2**) They coursed obliquely through the polyhedral cells to the basal membrane.

(**3**) They were seen between the basal epithelial cells attempting to penetrate the basal membrane.

Histological sections of the corneae revealed filling defects at the site of penetration of the *cercariae* into the epithelium (Fig. 3), compared with the control corneae.

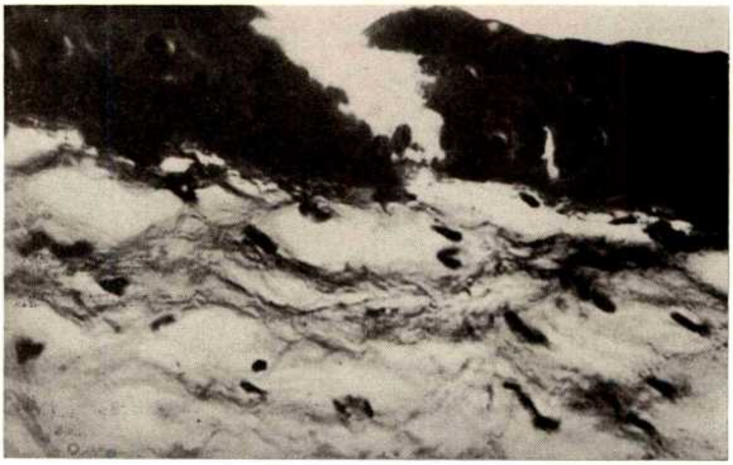

FIG. 3 *Filling defect at site of penetration of a* cercaria *through the corneal epithelium of a guinea-pig, reaching the basal membrane.* × 3,000

The *cercariae* penetrated the substantia propria of the trephined cornea only when the barrier of the basal membrane was artificially removed. The average time which elapsed for the *cercariae* to reach Descemet's membrane was 6·4 min. (Fig. 4). They did not penetrate Descemet's membrane. When the same procedure was repeated with the anterior segment of the guinea-pig eye, the *cercariae* took an average of 6·2 min. to reach Descemet's membrane, which was also not penetrated.

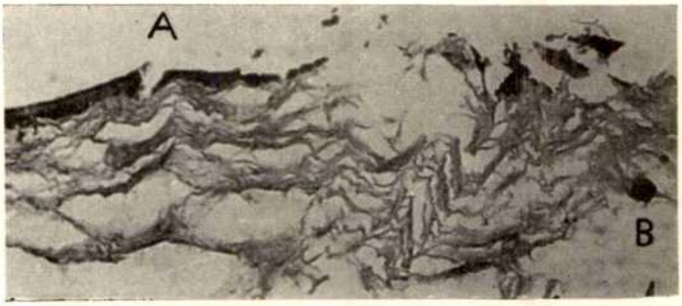

FIG. 4 *(a) Filling defect at site of penetration of a* cercaria *through the corneal epithelium of a guinea-pig. (b) Cross-section of* cercaria *penetrating the corneal substantia propria after induction of an experimental corneal ulcer.* × 550

SUBCONJUNCTIVAL INJECTION

The subconjunctival injection of *cercariae* into animals which were kept for from 3 to 6 months led to no ocular lesions, either early or late, as seen clinically and by serial histological sections; but the animals developed generalized schistosomiasis with enlargement of liver and spleen, and ascites was observed, especially in hamsters. The presence of lateral-spined *Schistosoma* ova were detected in thick liver smears, and were also seen by the dissecting microscope and in histological sections of the liver.

PRODUCTION OF SCHISTOSOMIASIS

Generalized schistosomiasis was also produced by the instillation of *cercariae* on to the conjunctival sac and eyelids. Adult *Schistosoma mansoni* worms were collected by perfusion of the liver and mesenteric vessels 45 days after instillation. Histological sections in part of the liver removed before perfusion revealed cross-sections of male and female *Schistosoma* worms, with the female lying in the gynaecophoric canal of the male (Fig. 5).

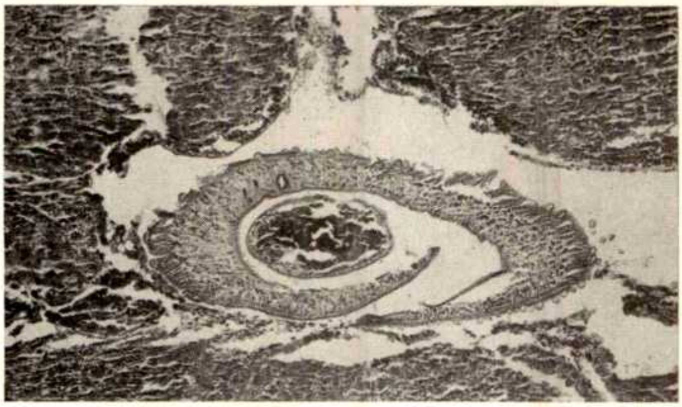

FIG. 5 *Histopathological section, showing adult male and female* Schistosoma mansoni *worms in liver of hamster, after instillation of* cercariae *into the conjunctival sac.* × 400

Serial histological sections of the eyelids and globes revealed no pathological changes.

OCULAR LESIONS

The injection of *cercariae* solution into the anterior chamber of guinea-pigs caused aqueous flare, keratic precipitates, and hypopyon formation. Histological section also revealed keratic precipitates and a mild leucocytic infiltration of the corneal lamellae. The animals showed no evidence of generalized schistosomiasis.

The eyes of animals injected with *Schistosoma mansoni cercariae* by the intraperitoneal route showed no lesions, either clinically or in serial histological sections.

Humans

The eyes of 150 patients suffering from schistosomiasis (Table VI) showed subconjunctival haemorrhages (12), and flame-shaped retinal haemorrhages (3).

Table VI *Ocular lesions in cases of* Schistosoma *infection*

Type of Schistosoma *infection*	*No. of cases examined*	*Subconjunctival haemorrhage*	*Retinal haemorrhage*
S. haematobium	67	5	–
S. mansoni	8	2	–
Combined (H and M)	11	1	–
Mixed (*Ascaris* and *Ankylostoma*)	64	4	3

Discussion

Hitchcock (1949) noticed that *cercariae* penetrated the skin in 2 to 15 min. and the ears in 2·5 to 8 min. Lewert and Lee (1954) stated that the basement membrane and ground substance acted as barriers to larvae, and demonstrated hyaluronidase-like activity from extracts of *cercariae* of *S. mansoni* which might aid in penetration. Hutchison (1928) stressed that the *cercariae* penetrated the subcutaneous lymphatic vessels, saying that within 6 weeks adult worms could be found in the liver and portal vein. Girges (1934) also stated that, as soon as the *Schistosoma cercariae* came into contact with the skin or mucous membrane, to which they are attracted by warmth, they pierced their way through to the lymphatics.

We found that the *cercariae* easily penetrated the skin of the eyelids and conjunctiva, the latter at a quicker rate. Their penetration *in vivo* was also quicker than *in vitro*, probably because they are attracted by the warmth of the living tissues. They did not penetrate the sclera probably because of its dense fibrous structure and avascularity.

They penetrated only the epithelial layer of the cornea, being presumably held back by the basal membrane, as Bowman's membrane is absent in mammals such as the rat (Duke-Elder and Wybar, 1961) and rabbit (Paton, 1955). However, they did penetrate the substantia propria, when the basal membrane was artificially removed. Similarly, they were held back by Descemet's membrane. Although the *cercariae* were clearly seen by the dissecting microscope and slit-lamp to penetrate the epithelium, their presence in histological sections was difficult to demonstrate; since their penetration is only superficial, they may drop out when the sections are prepared. The site of penetration was clearly seen histologically in the form of filling defects. We did not use fixatives such as Bouin's solution, which enable the *cercariae* to be fixed and adhere to the tissues (Standen, 1953), as we aimed at working under natural conditions.

De Queiroz (1961) found that *cercariae* penetrated the corneo-scleral limbus and the superficial corneal epithelium. He observed a *cercariae* passing through the basal membrane of the cornea in experimental animals after 40 min. instillation. He also noted that the *cercariae* could not penetrate the sclera.

We kept certain animals under observation until their general condition deteriorated. No ocular lesions were evident in any of them, but they developed generalized schistosomiasis. The result was the same when the *cercariae* were instilled on to the eyelid as when they were injected into the ocular tissues.

Thus, the local route of infection theory which was suggested as a cause for the development of ectopic schistosomal lesions, and favoured by Badir (1946), Kamel (1948), and Naim (1948), was not confirmed by our experiments.

The injection of a suspension of *cercariae* into the anterior chamber of guinea-pigs produced aqueous flare, keratic precipitates, and hypopyon formation, but failed to cause generalized schistosomiasis. De Queiroz (1961), on the other hand, found adult flukes in the liver after the injection of *cercariae* into the anterior chamber of the rabbit, but failed to detect them after subconjunctival injection.

The eyes of animals previously infected with *cercariae* of *S. mansoni* through the intraperitoneal route were unaffected, although they were kept for a long period until their general condition deteriorated from schistosomiasis. De Queiroz (1961) noticed lens changes in white mice, in the form of thickening of the anterior capsule with a granular deposit on the zonular lamella. He thought these might result from an increase in capsular permeability, perhaps through a toxic-allergic factor, from products elaborated by the adult worms.

Although subconjunctival and retinal haemorrhages were detected in few of the human patients examined, we still cannot be justified in saying that they were due to schistosomiasis as they were also seen in patients with mixed infections. No such lesions were evident in the experimental animals. El Tobgy and Wilson (1935) mentioned that, of 203 cases of schistosomiasis, not one showed "any abnormality in the eye". De Queiroz (1916) examined the eyes of 121 patients suffering from *S. mansoni* associated with other intestinal parasites, and although he found such lesions as chronic conjunctivitis, subconjunctival haemorrhages, keratitis, iritis, lenticular opacities, and retinal oedema, he stated that "it would be difficult to make *S. mansoni* specifically responsible for the ocular changes encountered". Massa and others (1965) observed pre-retinal haemorrhage, which they thought to be due to "vascular rupture caused by a fertilized egg of *S. mansoni*".

Various theories have been postulated as to the different routes by which the *Schistosoma* ova, or even the adult worms, can reach the systemic circulation and thereafter lodge in ectopic sites such as the eye. The presence of a patent foramen ovale was suggested, but lesions have been reported in patients in whom the foramen ovale was closed: *e.g.* *S. haematobium* in a branch of the left coronary artery (El Gazayerli, 1939); schistosomal myelitis (Bayoumi, 1939); schistosomal granulomata in the conjunctiva (Kamel, 1948).

Diamantis (1932) pointed out that *cercariae* develop to maturity and lay their eggs in the veins directly under the skin or mucous membrane through which they have penetrated, if the part is richly vascularized. Bilharz (1852) himself reported a lesion in the dorsal skin of a water carrier.

Day (1937), to explain the presence of these organisms in the lungs, stated that the gradual obstruction of the main portal channels in the liver by bilharzial cirrhosis, led to the opening up of various anastomotic channels, through which they might reach the lungs. Black (1945) suggested that the worms might pass against the blood stream, and that from the iliac veins and vena cava, they might ascend the scrotal, gluteal, and lumbar veins. Gama and Marques Sa (1945) explained the deposition of *Schistosoma mansoni* ova in the lower level of the spinal cord by the negative pressure in the epidural space. Faust (1948) described the vertebral venous system as a valveless plexus of vessels which intercommunicate with the vesical and haemorrhoidal veins, which are the normal habitat of adult *Schistosoma* worms. The ova in the vertebral venous system can thus spread to distant sites, without undergoing hepatic and pulmonary capillary filtration. Patson (1940) also stated that most cases of aberrant malignant metastasis, aberrant pyogenic metastasis, and aberrant embolism were spread through the vertebral venous system.

It has been found that the ova and adult *Schistosoma* worms can pass through the pulmonary capillaries under certain conditions in which there is no obstruction of the alveolar capillaries resulting in arterio-venous anastomotic channels. It has been proved experimentally that beads of 500 μ diameter, when injected into the pulmonary artery, can pass into the pulmonary vein and hence to the left side of the heart, after passing through the arterio-venous anastomotic channels in the lung (El Mofti and El Zawahry, 1962). This finding provides strong evidence that *Schistosoma* ova are able to pass from the right side of the heart to the left through the pulmonary capillaries, and helps to explain the aetiological problem of ectopic schistosomal lesions.

Summary

The injection of suspensions of *cercariae* subconjunctivally in animals did not cause ocular lesions, but produced generalized schistosomiasis. The instillation of *cercariae* on to the eyelids and conjunctiva also produced generalized schistosomiasis. Injection of *cercariae* into the anterior chamber of guinea-pigs resulted in an aqueous flare, keratic precipitates, and hypopyon, but generalized schistosomiasis did not develop.

The eyes of animals previously infected with *cercariae* of *S. mansoni* through the intraperitoneal route revealed no ocular lesions. The eyes of 150 patients suffering from schistosomiasis showed subconjunctival haemorrhages in twelve and flame-shaped retinal haemorrhages in three.

It is concluded from the experimental results that the theory of the local route of infection through the eye cannot account for ectopic schistosomal ocular lesions. Generalized schistosomiasis can be produced by cercarial penetration through either the eyelids or the conjunctiva. It is also concluded that schistosomiasis does not affect the ocular structures, except in the form of rare ectopic lesions.

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Scleral contact lens wear in unilateral aphakia

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It has been shown that the wearing of contact lenses prescribed for the optical correction of unilateral aphakia is not well maintained in patients fitted with either scleral lenses (Ruben, 1962; Bonnet, Gerhard, and Massin, 1966) or microcorneal lenses (Bonnet and others, 1966). Some of the causes for this failure of contact lens wear were analysed by Gerhard and Bronner (1965), who found that the failure rate was independent of the type of contact lens fitted.

In the patients who are unable to tolerate the contact lens because of irritation or who experience difficulty in its handling, it would be reasonable to expect that a more satisfactory long-term binocular visual result would be obtained by the use of an intraocular acrylic lens implant. Such an implant would have no advantage in patients intolerant of the lens because of heterotropia and, although the difference in retinal image size between the phakic and the correlated aphakic eye is reduced from an average of 6·99 per cent. with a contact lens to 1·92 per cent. with an intraocular lens (Girard, Friedman, Moore, Blau, Binkhorst, and Gobin, 1962), good binocular vision is usually achieved by either method. Girard and others (1962), including his co-author C. D. Binkhorst, therefore concluded that a contact lens should be tried first in all cases in preference to an intraocular lens, and this approach is now widely accepted.

However, Binkhorst and Leonard (1967), in reporting the results of 208 implantations of the iris-clip pseudophakos (Binkhorst, 1959), concluded that primary implantation of this device at the time of the cataract extraction is preferable to its secondary implantation, as surgical corneal dystrophy occurred in five eyes (7·1 per cent.) with secondary implantation and none with primary implantation. In a subsequent paper (Binkhorst, Gobin, and Leonard, 1969), it was stated that a contact lens should not be used to correct post-traumatic aphakia in children, because the authors considered that this reduced the chance of binocular re-education (Binkhorst and Gobin, 1967).

The justification for primary implantation of an intraocular lens to correct unilateral aphakia would be greater if it were possible to predict before the cataract extraction that successful contact lens wear was improbable. The present study, undertaken in an attempt to define factors which might militate against the successful wearing of a contact lens in unilateral aphakia, consists of the analysis of data relating to such patients fitted with a contact lens by one of us (E.M.T.L.) at the Cardiff Royal Infirmary between 1961, when the service was commenced, and the end of 1966.

Material and Methods

A circular and questionnaire were sent to the last known address of each patient with unilateral aphakia who was fitted with contact lenses at the Cardiff Royal Infirmary between 1961 and 1966 inclusive. Patients who failed to reply to the first circular were sent a further copy and those who

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still failed to reply were traced wherever possible by the staff of the Medical Research Council, Epidemiological Research Unit (South Wales). The patients' hospital records and contact lens notes were then examined to obtain other relevant information and this was collated with the replies to the questionnaire.

All patients who had their follow-up at the Cardiff Royal Infirmary subsequent to contact lens fitting were included in the study, even if the cataract operation had been performed elsewhere. Patients who attended the Cardiff Royal Infirmary for contact lens fitting only, having had both the cataract operation and subsequent follow-up elsewhere, were excluded from the study.

The patients were selected for contact lens fitting according to the criteria of the individual consultant surgeon but, with the exception of two cases, it is evident that the criteria included a visual acuity of at least 6/18 in the aphakic eye with the contact lens.

Patients were fitted with scleral lenses as a normal procedure in preference to micro-corneal lenses because of the ease of handling the large lens, the minimum risk of loss or damage and possible extra expense both to the patient and the National Health Service, and the great ease of fitting and supplying these lenses.

The scleral lenses fitted were all fenestrated minimum clearance impression lenses with double-curve optic and deep channel transition (Lewis, 1970). A micro-corneal lens was fitted initially in seven patients, five of whom were subsequently re-fitted with a scleral lens. The remaining two patients in this group were excluded from the study.

The patients were refracted with a contact lens *in situ* and impressions were made during the first appointment. The completed contact lens was usually supplied on the second visit and the follow-up continued over 5 months to ensure that the lens settled properly on the eye and that the patient was wearing it without difficulty. This required at least five report appointments, after approximately 2, 6, 10, 15, and 20 weeks.

Patients were requested to report back between appointments should difficulty be experienced and to make a new appointment should any problem arise subsequent to their discharge from the contact lens clinic. Many of the patients continued to attend the surgeon's clinics after discharge from the contact lens clinic.

Results

156 patients were reviewed (104 males and 52 females). The age distribution is shown in Table I and the period in years between the supply of the contact lens and the date of review in Table II. Within this group ten patients had died before the review, twelve could not be traced, and two had lost all useful vision in the aphakic eye, through secondary glaucoma and retinal detachment respectively.

Table I *Age and sex incidence in* 156 *cases*

Age (yrs)	*Male*	*Female*	*Total*
0–9	1	0	1
10–19	8	0	8
20–29	10	1	11
30–39	7	4	11
40–49	22	4	26
50–59	21	20	41
60–69	26	15	41
70–79	8	8	16
80–89	1	0	1
Total	104	52	156

Table II *Duration of follow-up in* 156 *cases*

Follow-up (yrs)	*Number of patients*	*Year when contact lens was fitted*
7	4	1961
6	28	1962
5	28	1963
4	30	1964
3	33	1965
2	33	1966

The remaining 132 patients reported that their use of the contact lens at the review date was as shown in Table III. This series includes 32 patients who had had a subsequent cataract extraction on the second eye, in eleven of whom the contact lens was no longer worn, but it should be noted that only two of the latter failed to wear the contact lens during the period of monocular aphakia.

Table III *Contact lens wear in 132 patients*

Contact lens wear at review date	*Number of patients*	*Per cent. of total patients*
6 or more hrs daily	53	54
Less than 6 hrs daily	15	
Worn after refit elsewhere	3	
No longer worn	61	46
Total	132	100

In all patients who had a cataract extraction on the second eye, the aetiology of the cataract was non-traumatic. These patients were excluded from further analysis, as they were no longer uniocular aphakics by the time of the review. The three patients successfully re-fitted with micro-corneal contact lenses elsewhere, having been unable to tolerate the haptic contact lens fitted initially, were also excluded since no detailed information was available relevant to these lenses. One further patient whose hospital records were unobtainable was also excluded.

There thus remained 96 patients fitted with a scleral contact lens for unilateral aphakia who retained useful vision in the operated eye at the review date. Table IV relates contact lens wear in this group to the aetiology of the cataract which required extraction irrespective of the duration of follow-up. The non-traumatic group includes cataract associated with chronic iridocyclitis, heterochromic cyclitis, diabetes mellitus, dystrophia myotonica and atopic eczema, senile cataract, unilateral congenital cataract, cataract following glaucoma surgery, and cataract following radiotherapy for a rodent ulcer.

Table IV *Contact lens wear related to aetiology in 96 patients available at the review date*

Aetiology of cataract	*Contact lens*		*Total cases*	
	Worn	*Not worn*		
Traumatic Penetrating	6	13	19	35
Non-penetrating	6	10	16	
Non-traumatic	35	26	61	
Total	47	49	96	

Though the numbers involved are necessarily small, patients who had sustained non-penetrating injuries did not wear their lenses substantially better than those who had penetrating injuries and therefore the traumatic group is considered as a single entity in subsequent Tables. It is also evident that those in the non-traumatic group wore their lenses considerably better than those in the traumatic sub-groups.

Table V indicates that this difference may be partly due to disparity in the duration of follow-up between the traumatic and non-traumatic cases. However, the same Table suggests that, in respect of the non-traumatic group, there is no appreciable reduction in the proportion of contact lenses worn after 2 years from the time of fitting, this being the minimum follow-up period in the sample studied. This is in direct contrast to the smaller traumatic group in which the proportion of contact lenses worn decreases the longer the follow-up period.

Table V *Contact lens wear related to duration of follow-up in 96 patients*

Follow-up (yrs)	*Contact lens*					
	Worn			*Not worn*		
	Traumatic	*Non-traumatic*	*Total*	*Traumatic*	*Non-traumatic*	*Total*
7	0	1	1	0	1	1
6	2	4	6	11	6	17
5	4	4	8	6	0	6
4	0	8	8	2	7	9
3	3	9	12	4	5	9
2	3	9	12	0	7	7
Total	12	35	47	23	26	49

Table VI relates contact lens wear to the age of the patient when the lens was supplied. Failure to maintain contact lens wear occurred in the majority of patients under the age of 50 years, irrespective of the aetiology of the cataract. Since younger patients are more numerous in the traumatic group, this age factor may also be relevant to the poor results obtained following trauma.

Table VI *Contact lens wear related to age in 96 patients*

Age (yrs)	*Contact lens*					
	Worn			*Not worn*		
	Traumatic	*Non-traumatic*	*Total*	*Traumatic*	*Non-traumatic*	*Total*
0–9	0	0	0	0	0	0
10–19	0	1	1	6	0	6
20–29	1	0	1	7	2	9
30–39	3	1	4	1	3	4
40–49	2	6	8	4	7	11
50–59	2	14	16	4	4	8
60–69	3	10	13	1	6	7
70–79	1	3	4	0	4	4
Total			47			49

Table VII (overleaf) relates contact lens wear to the sex of the patient. The slightly poorer overall results obtained in men are due to the much greater frequency of traumatic cataract in the male sex. The higher success rate in the male non-traumatic group compared with the female should be noted.

Table VII *Contact lens wear related to sex in 96 patients*

Sex	Contact lens Worn: Traumatic	Worn: Non-traumatic	Worn: Total	Not worn: Traumatic	Not worn: Non-traumatic	Not worn: Total
Male	9	21	30	21	12	33
Female	3	14	17	2	14	16
Total			47			49

Table VIII relates contact lens wear to whether the right or left eye was aphakic. In the non-traumatic group, patients with right aphakia maintained contact lens wear considerably better than those with left aphakia. This finding did not apply to the smaller traumatic group.

Table VIII *Contact lens wear related to right or left aphakia in 96 patients*

Aphakic eye	Contact lens Worn: Traumatic	Worn: Non-traumatic	Worn: Total	Not worn: Traumatic	Not worn: Non-traumatic	Not worn: Total
Right	5	21	26	13	11	24
Left	7	14	21	10	15	25
Total			47			49

Table IX relates contact lens wear to the visual acuity obtained in the aphakic eye with the contact lens. It is evident that the higher the visual acuity, the greater the proportion of patients maintaining contact lens wear, whether the aetiology of the cataract was traumatic or non-traumatic.

Table IX *Contact lens wear related to visual acuity of aphakic eye in 96 patients*

Visual acuity of aphakic eye with contact lens	Contact lens Worn: Traumatic	Worn: Non-traumatic	Worn: Total	Not worn: Traumatic	Not worn: Non-traumatic	Not worn: Total
6/4–6/5	4	11	15	3	4	7
6/6–6/9	8	21	29	13	19	32
6/12 or less	0	3	3	7	3	10
Total			47			49

Table X relates contact lens wear to the relative visual acuities of the aphakic eye with the contact lens and the phakic eye. As might be expected, the figures are very similar to those in Table IX.

Table X *Contact lens wear related to visual acuity in each eye in* 95 *patients*

Visual acuity of aphakic eye compared with phakic eye	*Contact lens*					
	Worn			*Not worn*		
	*Traumatic**	*Non-traumatic*	*Total*	*Traumatic*	*Non-traumatic*	*Total*
2 or more lines Snellen better	2	11	13	0	5	5
Within 2 lines Snellen	8	21	29	12	16	28
2 or more lines Snellen worse	1	3	4	11	5	16
Total			46			49

* 1 case omitted because of incomplete data

Table XI relates contact lens wear to the visual acuity in the phakic eye at the time of contact lens supply, which in the great majority of cases was the same as the visual acuity in that eye at the time of the contralateral cataract extraction. The relatively poor lens wear in patients with a high phakic visual acuity appears partly related to the preponderance of such patients in the traumatic group.

Table XI *Contact lens wear related to visual acuity of phakic eye in* 95 *patients*

Visual acuity of phakic eye	*Contact lens*					
	Worn			*Not worn*		
	*Traumatic**	*Non-traumatic*	*Total*	*Traumatic*	*Non-traumatic*	*Total*
6/4–6/5	2	5	7	11	8	19
6/6–6/9	9	24	33	11	13	24
6/12 or less	0	6	6	1	5	6
Total			46			49

*1 case omitted because of incomplete data

Table XII (overleaf) relates contact lens wear to the interval between operation and the time of contact lens supply. In one patient with a dislocated lens due to non-penetrating trauma, the time interval was calculated from the date of injury. The figures fail to provide support for the concept that early contact lens fitting after cataract operation favours successful long-term wear, but this may be due to patient selection. However, in the traumatic group, the four patients who had a contact lens supplied within 6 months of the original injury all continued to wear the lenses.

Table XIII (overleaf) lists the primary reasons given for failure to maintain contact lens wear in (a) the 26 patients in the non-traumatic and (b) the 23 patients in the traumatic group.

Table XII *Contact lens wear related to fitting delay in* 96 *patients*

Interval from operation to contact lens supply	*Contact lens*					
	Worn			*Not worn*		
	Traumatic	*Non-traumatic*	*Total*	*Traumatic*	*Non-traumatic*	*Total*
Less than 6 mths	8	23	31	13	20	33
6 mths or more	4	12	16	10	6	16
Total	12	35	47	23	26	49

Table XIII *Reason for failure of contact lens wear in* 49 *patients*

Reason given for failure	*No. of patients*	
	Non-traumatic	*Traumatic*
Irritation	6	11
Diplopia	3	4
Binocular difficulties without diplopia	3	3
Fogging of lens	3	—
Occupation	1	2
Difficulty in handling lens	4	—
No subjective benefit	2	2
Cosmetic	1	—
Lens lost	2	1
No reason given	1	—
Total	26	23

(*a*) One patient with diplopia had a manifest divergent strabismus which was not completely eliminated before contact lens fitting in spite of two operations for its correction. One patient with binocular difficulties in the absence of diplopia had also had an operation for the correction of a manifest divergent strabismus before contact lens fitting. Excessive mucus secretion probably accounted for fogging of the lens in one patient, but the precise cause was unknown in the other two patients with this symptom. One patient, a marine fitter, discontinued wearing the contact lens because of the dust associated with that occupation. Of the four patients with lens handling difficulties, one had arthritis and two never mastered the basic techniques. The patient giving a cosmetic reason was a female typist aged 32 years who did not like the look of the haptic lens, but it should be noted that a micro-corneal lens fitted initially was also unacceptable.

(*b*) Three of the four patients with diplopia had a manifest strabismus before contact lens fitting. Of these one had an operation for correction of the deviation before the contact lens fitting and two had similar operations after the fitting, one of the latter having two such operations. The two patients giving occupational reasons comprised one who experienced irritation from fumes on starting new employment at a chemical factory and one who found working in a ship's boiler room caused irritation.

Discussion

The results of this investigation confirm the findings of previous authors (Ruben, 1962; Bonnet and others, 1966) that long-term wear of a scleral contact lens is not achieved in a high proportion of patients with unilateral aphakia. In the present study, of the 134 patients who were alive and could be traced, 46 per cent. were no longer wearing their contact lens, though nine of them had worn one successfully before cataract extraction in the second eye.

Contact lens wear was better maintained if the aetiology of the cataract was non-traumatic and if a good visual result was obtained in the aphakic eye, particularly if the acuity in that eye was better than in the phakic eye (see Maurer, 1962). In the non-traumatic group, patients aphakic in the right eye wore their lenses considerably better than those in the left eye, possibly because of the factor of eye dominance (Welsh, 1961). Patients over the age of 50 years tended to do better than younger patients, and in the non-traumatic group men maintained their contact lens wear better than women. Delay in fitting the contact lens after cataract surgery appeared to have no detrimental effect in the group studied. The four patients in the traumatic group who were supplied with a contact lens within 6 months of the injury all maintained contact lens wear in spite of the poor overall results in that group, but the feasibility of such early fitting was probably indicative of less severe trauma (see Foley, 1954).

Possibly because of patient selection, diplopia and other binocular difficulties comprised only a small proportion of the reasons for discontinuing contact lens wear. A manifest preoperative deviation, however, especially if severe enough to warrant strabismus surgery, carried a poor prognosis.

In spite of these findings, it would not appear possible to predict preoperatively in the individual patient undergoing cataract surgery that postoperative contact lens wear will not be maintained. It should also be noted that the aphakic visual acuity and therefore the relative acuities of the aphakic and phakic eye cannot be predicted at that stage, though they appear relevant to the success of subsequent contact lens wear.

Schirmer (1963a) reported that patients with a low corneal sensitivity to both pressure and friction, as tested with a specially designed Aesthesiometer (Schirmer, 1963b) using a large contact surface, tolerated contact lenses significantly better than patients with a high corneal sensitivity. Unfortunately, this technique would not seem applicable to patients about to undergo cataract section with the consequent division of corneal nerves and reduction in corneal sensitivity.

Because of the potential complications of an intraocular acrylic lens implant (Troutman, 1962; Choyce, 1964; Bresnick, 1969), we are firmly of the opinion that the insertion of an intraocular lens as a primary procedure is not warranted in patients who, at the time of preoperative assessment, seem suitable for contact lens fitting. However, if contact lens fitting appears to be inappropriate, for example on account of potential difficulty in handling the lens, the insertion of an intraocular lens at the time of cataract surgery (Binkhorst and Leonard, 1967) probably merits wider consideration than it has hitherto been accorded.

Though such a procedure may conveniently resolve the binocular problems created by unilateral cataract extraction, it can subsequently produce the very same predicament should cataract extraction become necessary on the second eye. The obvious course is to fit an intraocular lens in the second eye but technical difficulties may prevent this being achieved. The presence of less severe cataract in the second eye at the time of the initial cataract extraction may therefore be a further contraindication to primary intraocular lens implantation.

In spite of these considerations and the undoubted risks incurred when placing such implants in the eye, the long-term results of contact lens wear in unilateral aphakia offer no cause for complacency, and substantial improvement should be obtained by using a proportion of intraocular lens implants if the results of Binkhorst and Leonard (1967) can be reproduced.

The opportunities for primary implantation of such intraocular lenses in the treatment of traumatically-induced cataract must be few and almost invariably associated with greater risks than in the non-traumatic group. For these reasons there is rarely any necessity to consider such a procedure and secondary implantation can always be undertaken in suitable cases should a trial of contact lens wear prove unsuccessful.

Summary

A retrospective study of 156 patients fitted with scleral contact lenses for the optical correction of unilateral aphakia between 1961 and 1966 inclusive was made at the end of 1968 and the findings are analysed. It was not found possible to define factors by which the failure to maintain such contact lens wear could be confidently predicted in the individual patient before the cataract extraction. The possible indications for primary implantation of an intraocular acrylic lens are discussed in the light of these results.

Our thanks are due to Messrs. M. V. Graham and P. A. Graham for kindly allowing the inclusion of their patients in this study and to Prof. A. L. Cochrane, Director of the Medical Research Council, Epidemiological Research Unit (South Wales), whose staff assisted in tracing patients.

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Traumatic fracture of contact lens with corneal injury

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There are few reports of the action of contact lenses modifying the effects of injury to the eye. The increasing popularity of contact lenses and the growing risk of serious road accidents have suggested the publication of this case in which traumatic fracture of a contact lens caused a moderately severe and unusual corneal injury.

Case report

A Danish girl aged 19 was involved in a road traffic accident in December, 1969. At the time of the accident she was wearing plastic corneal contact lenses for the correction of simple myopia. She was unconscious for some time and later could give no details of exactly what happened other than that she was the front seat passenger and not wearing a safety belt.

Examination

There was a partial thickness laceration of the right cornea at the junction of the middle and lower thirds extending in an irregular horizontal line from side to side. From the depth of this laceration the cornea was split to the lower limbus and in the lamellar pocket so formed were embedded multiple fragments of a shattered corneal contact lens. At no point did this lamellar laceration penetrate the full thickness of the cornea. Above this wound and towards the nasal side of the cornea was a smaller, partial thickness laceration of the cornea, also containing fragments of contact lens and again not penetrating the full thickness of the cornea. There was also an irregular conjunctival laceration temporal to the limbus and a small hyphaema. There were also multiple lacerations of the eyelids and face most of which contained fragments of shattered windscreen. The left eye was uninjured.

Operation

That same evening the right corneal lacerations were sutured and with the aid of the operating microscope as many as possible of the fragments of contact lens were removed from the lamellar pocket in the cornea. Fragments of contact lens were also removed from the right upper fornix. An intact contact lens was removed from the left eye which was undamaged. The various lid and facial lacerations were sutured after removal of the shattered windscreen fragments.

Result

The patient made an uninterrupted recovery, the lid and facial sutures being removed on the fourth day, and the corneal sutures on the tenth day.

Follow-up

After 7 months the findings were as follows:

RIGHT EYE Visual acuity 6/9, with −5 D sph.

LEFT EYE Visual acuity 6/6, with −4·75 D sph.

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The right cornea had healed satisfactorily, leaving an irregular, horizontal, partial-thickness scar, passing across the lower part of the pupil with some very small fragments of contact lens still embedded in the stroma (Figure). The eye was white and quiet and the patient symptom free.

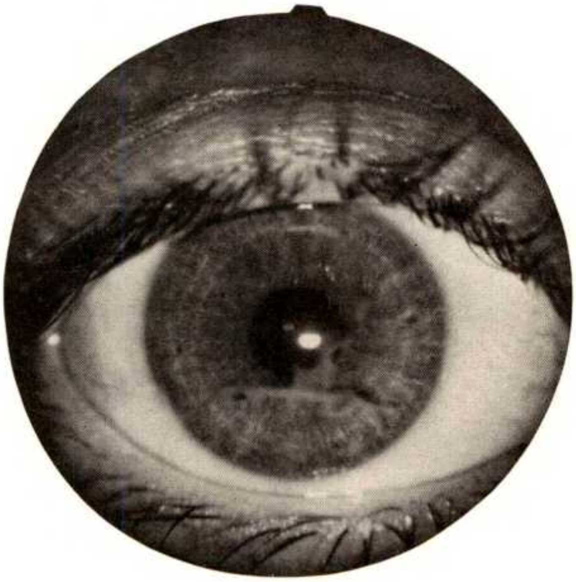

FIGURE *Appearance of the injured eye 7 months after operation*

Comment

Previous reports of a fractured contact lens modifying the effects of eye injury include three cases of corneal abrasion of an eye with a contact lens caused by a blow from a fist (Brown, 1964). In each case the lens broke into several large pieces only, those remaining in the eye were always found in the upper fornix, and the abrasions healed rapidly and completely without visual loss.

There is one reported case of traumatic dislocation of a contact lens into the eyelid, again caused by a blow from a fist (Shenken, 1969). In this case the contact lens was "lost" for 40 months after the injury, the patient experiencing only mild intermittent conjunctivitis. Finally a swelling of the outer upper eyelid developed and an intact corneal contact lens was removed from within the tissues of the eyelid by incision from the conjunctival surface. A similar case of a contact lens "lost" for a year and eventually found embedded in the tissues of the upper eyelid and needing surgical removal has been reported (Michaels and Zugsmith, 1963), but with no mention of trauma as a precipitating cause.

A most unusual case following severe injuries to the trunk and face with extensive skull and facial fractures was reported by Podos and Freeman (1965). The eyelids were swollen and ecchymotic except for a central round clear area in one upper lid which was found to overlie a contact lens trapped between the lid and globe. The cornea was uninjured. It was postulated that the presence of a contact lens between the globe and the lid prevented blood flowing into the lid over the lens thus maintaining a circular blood-free area. This was suggested as a diagnostic sign in head trauma with wearers of contact lenses.

On the other hand protection of the eye by a contact lens from possible severe injury has also been reported. Györffy (1951) described four such cases: in one a high-velocity metal splinter lodged in a contact lens without fracturing it and without causing ocular damage, in another the contact lens was badly scratched by a thorn without ocular damage, and in two cases fist injuries led to severe periorbital haematoma (with loss of consciousness in one) without corneal injury or fracture of the lenses. Three other cases reported by Brown (1964) included a contact lens cracked right through by a high-velocity shotgun pellet without corneal injury, a high-velocity metal splinter penetrating a contact lens and causing a partial-thickness laceration of the stroma which healed with minimal scarring, and corneal abrasions of an aphakic eye with fracture of the contact lens when it was struck by a nail.

In the present case one can only speculate that the patient's head struck the windscreen violently, embedding the lower edge of the contact lens in the cornea, and that the divergence of the stress by the contact lens shattered it before the cornea was completely perforated.

Summary

A case of traumatic fracture of a contact lens with corneal injury is presented together with a review of the literature.

The photograph was taken by Mr. P. Broadberry, Department of Medical Photography, Queen Victoria Hospital, East Grinstead, Surrey.

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Origin of spectacles in India

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The European records of the origin of spectacles are very controversial. The suggestion that spectacles were first invented during the 13th century in Italy by an unknown layman of Pisa is not convincing, because there are also references to spectacles in Hindu literature at about the same time.

In the life of Vyasaraya (1446–1539), written in Sanskrit by his contemporary, the poet Somnath, the 74-year-old Vyasaraya is described as using a pair of "spectacles"* to read a book in 1520 A.D. at the Court of King Krishna Deva Raya, one of the rulers of the Vijaynagar Empire (1336–1646). The Portuguese traders, well known to Vyasaraya, arrived in India in 1498 and were established in Goa in 1510. Gode (1947) referred to by Pendse (1954) assumed that the Portuguese presented spectacles amongst other gifts to Vyasaraya, but this does not necessarily mean that the Portuguese introduced spectacles into India.

It is claimed that in Ceylon, during the reign of Bhuvanaikabahu IV (1344—1353), lenses and spectacles were made by Devanarayan, an Indian architect, who was originally commissioned from India to build a Buddhist monument at Gadaladeniya. Since this monument is in the Vijaynagar style of architecture, it would confirm that Devanarayan came to Ceylon from the Hindu Empire of Vijaynagar. He must have known the art of spectacle-making in India before he went to Ceylon, and this means that the Vijaynagar courtiers must have known the use of spectacles before the arrival of the Portuguese at the end of the 15th century.

Quartz crystals were used for manufacturing spectacle lenses in a South Indian town near Tanjore, which was taken by the British in 1771. It is interesting that Oppert (1907) also mentioned a South Indian Hindu caste which possessed polished crystal lenses. It is significant that in the South Indian languages the terms for spectacles are very different from those of North India. In the Kannada language of Mysore, South India, the term "Kannadak" is used for spectacles, and two other South Indian languages, *i.e.* Malayalam and Tamil, use similar words to describe spectacles.

The widespread use of spectacles for presbyopia can be inferred from the popular terminology for spectacles in certain parts of India: *e.g.* "Chaleesi" and "Chalesa" meaning "forty" in Maharashtra and Orissa, "Chatwar" meaning "fourth decade" in Andhra, and "Betalan" meaning "forty-two" in Gujarat. Ramdasa (1608–82) used the word "Chalasi" to describe spectacles, and requested contemporary scribes to use middle-sized letters to write their manuscripts. This would imply that the use of spectacles was perhaps confined to certain classes, *e.g.* the Brahmins.

* The term used is "upa-lochana" (substitute or secondary eyes), "upa" being a Sanskrit prefix loosely meaning substitute or secondary which was widely used in Sanskrit, *e.g.* the "Vedas" and the "upa-Vedas". A Marathi poet Vamanpandita (1636–95) used the term "upa-netra" (netra meaning eyes) for spectacles. It would, therefore, be incorrect to assume that the term "upa-lochana" was specially coined to describe foreign spectacles.

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The agents of the British East India Company (which received the Royal charter in 1600 A.D.) have been incorrectly credited by some writers with introducing spectacles into India. There is a reference (in a letter dated September 22, 1616, from an English firm "Kerridge, Barker, and Mittford") to the slow sale of English spectacles in Rajputana, the modern state of Rajsthan in North India. There are references to spectacles in the Hindu literature much earlier than this, and spectacles are also depicted in some of the Mughal miniatures. The ancient Indian spectacles generally had carvings of a deity, and perhaps Indians at that period did not want to use non-Indian spectacles, which may account for the slow sale of the English importations.

Summary

The account of Devanarayan (between 1344–1353), the use of spectacles by Vyasaraya (1520 A. D.), the indigenous manufacture of spectacle lenses in South India, the different terms used for spectacles in the North and South Indian languages, and other historical facts all indicate that spectacles were invented in India, in all probability by the Kannada-speaking Hindus. It is therefore most likely that the use of lenses reached Europe *via* the Arabs, as did Hindu mathematics and the ophthalmological works of the ancient Hindu surgeon Suśruta.

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Lactic dehydrogenase activity of aqueous humour in retinoblastoma

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Lactic dehydrogenase (LDH) is an enzyme that catalyses the reversible reaction:

$$\text{Pyruvate} + \text{NADH} \rightleftarrows \text{NAD} + \text{Lactate}$$

NAD = nicotinamide adenine dinucleotide
NADH = reduced nicotinamide adenine dinucleotide
LDH can also react with NADP.

Although the levels of LDH have been estimated in the aqueous humour of animals (Kuhlman, and Kaufman, 1960), information regarding LDH levels in human aqueous humour appears to be scanty.

It is known that malignant tumours at different sites in the body are associated with an increased LDH activity in the corresponding body fluid (Wroblewski, 1957).

The purpose of the present study is to determine whether there is an increased LDH activity in the aqueous humour in cases of intraocular malignancy.

Materials and methods

Specimens of aqueous humour were collected from fifty patients coming for surgery to the Victoria Memorial Eye Hospital, Colombo. Of these, 46 had non-malignant intraocular disorders and four had retinoblastomata. The non-malignant intraocular disorders included the following:

Cataract	33	Anterior staphyloma	3
Adherent leukoma	4	Lens-induced glaucoma	2
Aphakia	3	Retinal detachment	1

The aqueous humour was collected using an Amsler's needle connected to a dry 2 ml. syringe, which was introduced at the limbus. These specimens of aqueous humour and blood were kept at 4°C and were analysed within 24 hours of collection.

The LDH activity in both aqueous humour and blood was estimated by the colorimetric method of King (1959). The principle of estimating the enzyme was first described by Wacker, Ulmer, and Vallee (1956), where lactate and NAD are used as substrates and the increase in the optical density at 340 mμ is measured. The advantage of this technique is that the reagents are stable and cheap.

A unit of activity is the amount of LDH which will reduce 1 μmole lactate to 1 μmole pyruvate in 15 minutes at 37°C. Activity is expressed in units per 100 ml. of specimen.

The volume of aqueous required for the estimation is only 0·1 ml. and sufficient aqueous humour was obtained even from patients with a shallow anterior chamber. Care was taken to see that none of these specimens was contaminated with blood.

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Results

The LDH activity in the aqueous humour of the 46 non-malignant cases varied from 0 to 350 units/100 ml. (Table I).

Table I *LDH Activity in 46 patients with non-malignant intraocular disorders*

Diagnosis	*Number of patients*	*Range of LDH activity (units/100 ml.)*	
		Serum	*Aqueous humour*
Cataract	33	230 to 470	Nil to 350
Adherent leucoma	4	150 to 240	Nil to 160
Aphakia	3	160 to 480	Nil to 80
Anterior staphyloma	3	400 to 420	40 to 160
Lens-induced glaucoma	2	250 and 400	240 and 190
Retinal detachment	1	160	180

The LDH activity in the serum collected and estimated simultaneously varied between 150 and 470 units/100 ml. The normal range is 160 to 400 units/100 ml. (King, 1959).

The four cases of retinoblastoma investigated gave the results shown in Table II. They all had a white mass behind the pupil which was clinically diagnosed as a retinoblastoma. Subsequent microscopic examination confirmed the diagnosis in all of them.

Table II *LDH Activity in 4 cases of retinoblastoma*

Age (yrs)	*Sex*	*LDH Activity (units/100 ml.)*	
		Serum	*Aqueous humour*
1½	M	380	3,250
2½	M	380	1,800
3	F	280	2,100
3	M	480	2,660

Discussion

Since it was not possible to estimate the LDH levels in the aqueous humour of normal human eyes, these were estimated in the above 46 patients with non-malignant intraocular disorders.

The highest value obtained was 350 units/100 ml. in a patient with a cataract who had a pseudoexfoliation of the lens capsule. The lowest value obtained from a case of retinoblastoma was more than six times this value.

These results indicate that retinoblastomata are probably associated with a gross elevation of LDH activity in the aqueous humour.

Non-malignant growths are not associated with increased LDH activity (Erickson and Morales, 1961). The LDH activity in the body fluid bathing a non-neoplastic lesion in a patient is lower than the LDH activity in the serum of that patient (Wroblewski, 1957). Disorders such as primary hyperplastic vitreous and intraocular tuberculosis, which may simulate a retinoblastoma, are therefore unlikely to be associated with gross elevations of LDH activity in the aqueous humour. It would seem, therefore, that the estimation of the LDH activity in the aqueous humour might be of value in the diagnosis of retinoblastoma.

Summary

LDH activity in the aqueous humour of 46 patients with non-malignant intraocular disorders ranged from 0 to 350 units/100 ml.

The four cases of retinoblastoma studied gave values of 1800, 2100, 1600, and 3250 units/100 ml.

Since LDH activity in the aqueous humour is greatly elevated in retinoblastoma, it seems likely that the estimation of LDH activity in the aqueous humour may be of value in the diagnosis of intraocular malignancy.

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Changes in the anterior segment as a presenting feature in leukaemia

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Involvement of the anterior segment in leukaemia is thought to be common, although it is often slight and easily overlooked (Allen and Straatsma, 1961). The following patient came for consultation because of changes in the anterior segment, and although apparently quite healthy she was in the early stages of leukaemia and was soon to succumb from the overt disease.

Case Report

A married woman aged 81 years was referred by her general practitioner who was treating her for a corneal ulcer on the right eye. Her general health was good apart from a mild gastric upset a few weeks previously.

OCULAR EXAMINATION

Day 1

Visual acuity : 6/24 both eyes unaided.

Right eye : A ring ulcer 1 mm. from the limbus stained positively with fluorescein. There were small infiltrates at the limbus, above and temporally and below. The anterior chamber was clear, with posterior polar lens opacities.

Left eye : The anterior segment was normal apart from posterior polar lens opacities.

Day 2

Right eye : The numbers of infiltrates increased, some of them being large, extending towards the centre, and also raising the conjunctiva peripherally. Corneal oedema, folds in Descemet's membrane, and a moderate flare in the anterior chamber were observed.

ADMISSION TO HOSPITAL

She was admitted for investigation and intensive treatment. A hyphaema developed in the right eye and the eyelids became oedematous on both sides.
She had irregular pyrexia and tended to be restless. She was obese and anaemic-looking, with a few petechiae on the arms and chest. No other abnormality was noted.

LABORATORY INVESTIGATIONS

Haemoglobin 62 mg. per cent.; white cell count 116,000/mm.^{3} (33 per cent. myeloblasts). Sternal marrow 81 per cent. myeloblasts.

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Address for reprints: G. N. Bhadresa, F.R.C.S., 25 Gatesheath Drive, Upton-by-Chester, CH2 1QU.

Day 3

There was a subconjunctival haemorrhage in the right eye, which was treated with prednisolone 50 mg./day and Myeleran 4 mg./day.

Day 4

Infiltrates were also seen at the limbus in the left eye.

TERMINATION

Her general condition was improving, when on the 15th day she suddenly went into cardiac failure and died.

Post mortem EXAMINATION (Figs 1 to 3)

The liver, spleen, kidneys, and heart were normal in size and weight. Sections of pericardium, myocardium, liver, spleen, lungs, and kidneys showed capillaries filled with myeloblasts. Sections of both eyes showed heavy cellular infiltrates at the limbus and adjoining superficial corneal stroma with scarring and indentation. The anterior chamber contained serous exudates and clumps of large basophilic cells with indented nuclei deposited on the posterior corneal surface. The trabeculae and canal of Schlmem, iris, and ciliary body were infiltrated, and the retinal vessels, and those at the disc and optic nerve, were choked with similar cells. Leukaemic infiltration was also present in the scleral channels, attached muscles, Tenon's capsule, and the episcleral tissues.

Discussion

Foster Moore (1925), in an analysis of 138 cases of leukaemia of all types, observed that, while 87 per cent. showed retinal changes, external changes were infrequent; these included slight ptosis, subconjunctival haemorrhages, ecchymosis of the lids, and proptosis.

Allen and Straatsma (1961), in a pathological examination of 76 eyes, observed that almost half showed ocular involvement, which was more common in acute cases. Scleral and limbal abnormalities were common, but were slight and easily overlooked. The most frequent sign was slight thickening of the epibulbar tissues near the limbus, occasionally progressing to gelatinous yellow or flesh-coloured nodules. In no case was the central cornea involved. Corneal ulceration was not mentioned in any of these cases.

In a case of acute myeloblastic leukaemia reported by Jamotton, Massa, de Vloo, and Fievet (1963) in a patient aged 34 yrs, the anterior segment appeared to be normal, although there was infiltration into the choroid, retina, and optic nerve with papilloedema.

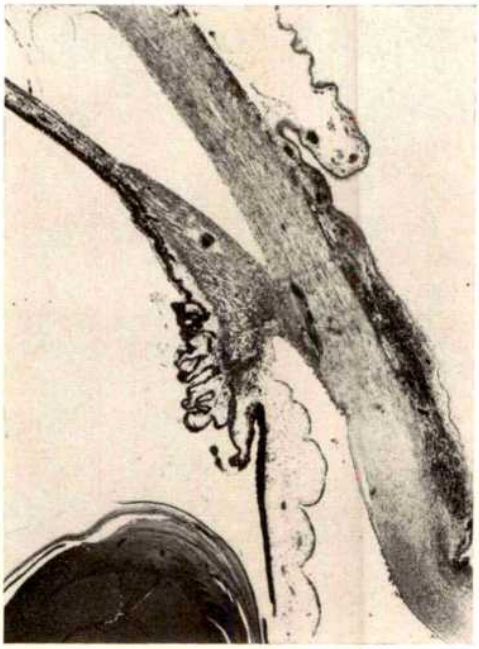
Of four fatal cases of leukaemia observed by Hocking and McTaggart (1963), one had a cataract extraction, but died after the operation of acute myeloblastic leukaemia; this patient does not appear to have had changes in the anterior segment.

Summary

The case is described of a patient who presented with a corneal ulcer and infiltrates, who shortly died of acute myeloblastic leukaemia.

I wish to thank Mr. W. D. Hopkins, consultant ophthalmologist, for permission to publish this case. The preparation of the histological sections and the pathological report by Prof. Norman Ashton of the Institute of Ophthalmology, are gratefully acknowledged.

(1)



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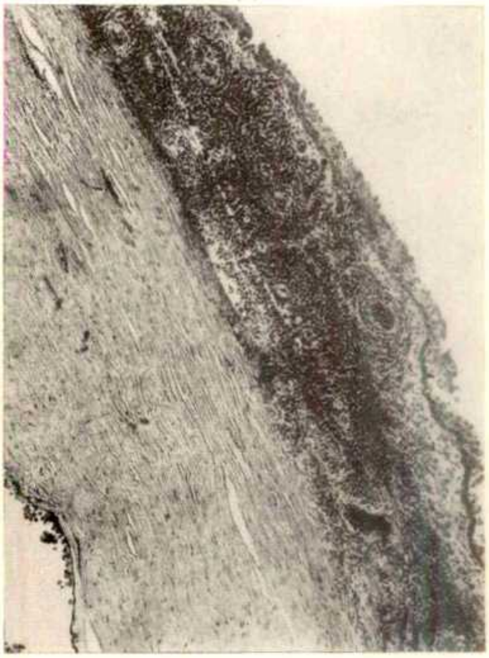

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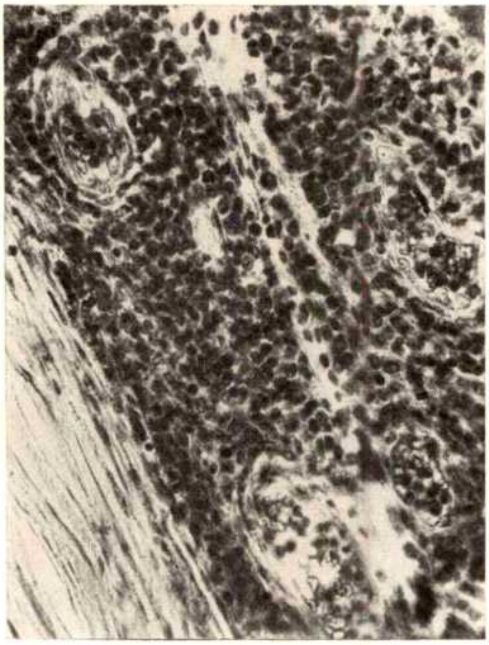

FIG. 1 *Heavy cellular infiltration at the limbus; superficial corneal ulcer; deposition of cells on the posterior corneal surface* ×17

FIG. 2 *Heavy subconjunctival infiltration at the limbus* ×60

FIG. 3 *Intravascular and perivascular infiltration by myeloblasts* ×250

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Brit. J. Ophthal. (1971) **55**, 136

Gas gangrene panophthalmitis

S. K. BHARGAVA AND A. CHOPDAR*

West of England Eye Infirmary, Exeter

Gas gangrene infection of the eye is a rare complication in civilian life. Leavelle (1955) made an extensive review of 53 cases published since 1904 and added three of his own, and five more cases have been reported (Arnold, 1955; Oehring and Jütte, 1963; Walsh, 1965; McEntyre and Curran, 1968; Kurz and Weiss, 1969), bringing the total to 61.

In all the cases so far reported the gas gangrene has followed a perforating wound of the globe, mostly in association with an intraocular foreign body. All developed a fulminating panophthalmitis despite vigorous therapeutic measures and in no case could the eye be saved. There is no record of any systemic dissemination from gas gangrene panophthalmitis.

Case report

A 49-year-old man was seen in the outpatients' department of the West of England Eye Infirmary, with a painful swollen eye and rapid loss of vision.

He gave a history of "something flying into his left eye" about 20 hours previously. He had been trying to free a bolt from his car wheel by driving it out with a blunt-ended iron rod and hammer, and as he struck the head of the rod with the hammer he felt something hit his eye. The eye gave him little trouble until late that night, when he had some pain and blurred vision.

Examination

He was of average build and appeared pale and ill. The pulse rate was 80/min. regular; respiration 18/min.; temperature 100·8°F.

The visual acuity of the right eye was 6/6, but the injured left eye had only perception of light. The lids of the left eye were grossly oedematous and tense. There was marked conjunctival chemosis and considerable limitation of ocular movements in all directions. The eyeball was proptosed and felt hard on gentle palpation. The cornea was hazy and showed a small penetrating laceration 3 mm. in length about 3 mm. from the limbus at the 5 o'clock position. A tag of iris was incarcerated in the wound, which by that time was reasonably well sealed. The anterior chamber was shallow and its contents were turbid and brownish in colour. The most striking feature was the presence of a small air bubble in the anterior chamber. The lens was damaged and opaque. On ophthalmoscopy there was no red reflex and fundus examination was not possible.

Slit-lamp examination showed an oedematous cornea with most haze around the wound edges, and flare and many cells in the brownish turbid exudate in the anterior chamber.

Investigations

RADIOLOGY

X-ray of the left orbit revealed a small radio-opaque metallic foreign body lying deep in the globe.

BACTERIOLOGY

Two swabs were taken from the conjunctival sac for culture on admission — one for aerobic and the other for anaerobic organisms. The following report was received 24 hrs later.

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Address for reprints: S. K. Bhargava, West of England Eye Infirmary, Magdalen Street, Exeter, Devon EX2 4HT
* Present address: Royal Eye Hospital, St. George's Circus, London, S.E.1

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1. *Brit. J. Ophthal.* (1955), **39,** 557
2. *Brit. J. Ophthal.* (1956), **40,** 159
3. *Brit. J. Ophthal.* (1965), **49,** 98

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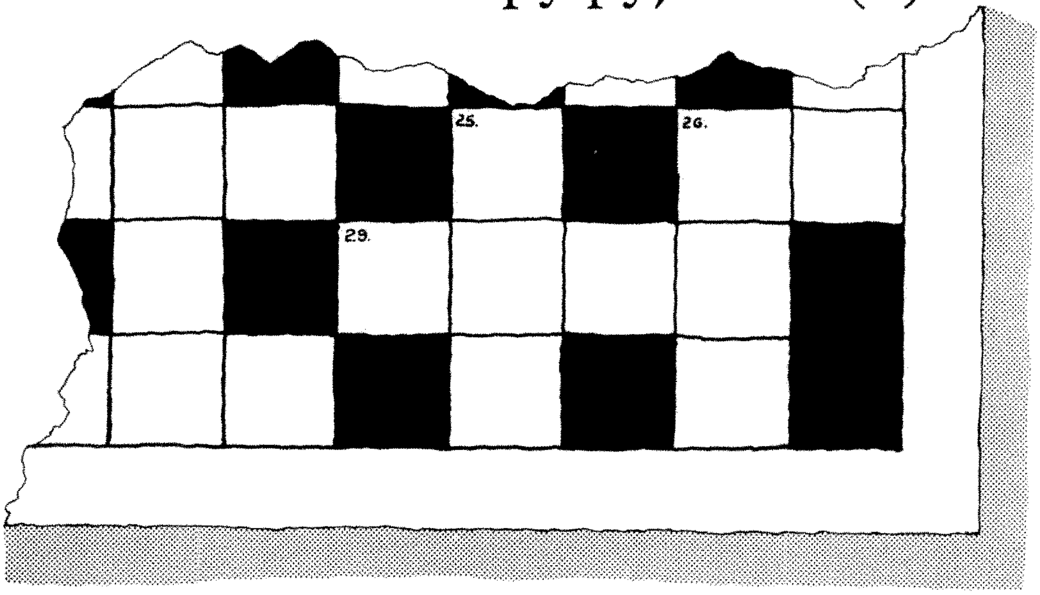

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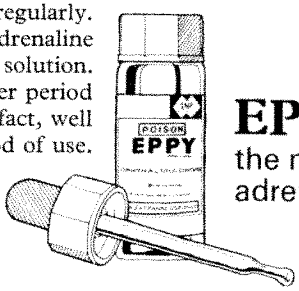

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"Culture sterile for aerobic organisms, but suspicious growth in the anaerobic medium".

Within the next 24 hours a growth of *Clostridium welchii* was confirmed, which was sensitive to tetracycline and penicillin.

Treatment

As an emergency measure, the patient was given tetanus toxoid 0·5 ml. and tetracycline 100 mg. intramuscularly. An attempt was made to remove the intraocular foreign body with a magnet, but this proved unsuccessful. The iris was freed from the corneal wound and abscised. The corneal laceration was stitched and soframycin 500 mg. was injected subconjunctivally after the operation. Intramuscular tetracycline 100 mg. was continued every 6 hours.

On the second day the patient's condition did not improve and after considering the bacteriological report of suspected growth of anaerobes the antibiotic was changed to crystalline penicillin 1,000,000 units intramuscularly every 6 hours. The ocular concentration was reinforced by giving it subconjunctivally.

On the fourth day a ring abscess formed on the cornea and the anterior chamber contained frank pus but there was no further gas formation; the eye, however, had become blind. By the fifth day there was a fully-developed panophthalmitis, the oedema of the lids and conjunctival chemosis had worsened, and the patient's temperature still varied about 100°F.

It was decided to eviscerate the globe. The contents of the globe were found to be purulent and brownish in colour, but no gas bubbles were present. A specimen of the contents was sent for culture and was later reported as sterile. Systemic intramuscular penicillin was continued postoperatively.

Result

The recovery after evisceration was remarkable. The temperature returned to normal on the second postoperative day. The lid oedema and conjunctival chemosis had settled considerably by the third day and the socket remained clean and uninfected. The patient was given penicillin orally, continued to improve, and was discharged from hospital on the seventh postoperative day.

Comment

The brownish turbid contents of the anterior chamber and the presence of an air bubble in a comparatively hard injured eye with a retained contaminated intraocular foreign body, produced a typical picture of gas gangrene endophthalmitis, which rapidly progressed to fulminating panophthalmitis necessitating evisceration (Duke-Elder, 1954). As in other reported cases, there was no systemic dissemination and the toxins were confined within the globe.

Once gas gangrene ophthalmitis is obvious, no treatment has yet been found effective to save the eye, and in this case also the antibiotics did not alter the ultimate course leading to the loss of the eye. However, the culture from the eviscerated contents of the globe was found to be free of anaerobes as well as aerobes. It seems that, although the antibiotics were effective in eliminating the *Clostridium welchii* organisms, the toxins produced rapid and severe necrosis of the ocular tissues.

Summary

A case of penetrating injury of the eye with retained intraocular foreign body, complicated by *Clostridium welchii* infection, is reported and the patient's day-to-day progress described. The inexorable development of panophthalmitis necessitated the evisceration of the globe. The postoperative course was uneventful and the healing of the socket was satisfactory.

We wish to thank Mr. F. J. Rutter for permitting us to study and report this case.

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Brit. J. Ophthal. (1971) **55,** 139

Gas gangrene panophthalmitis treated with hyperbaric oxygen

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Gas gangrene panophthalmitis is a rare and serious complication of penetrating injury of the eye. Since 1904, 61 cases have been described in the literature (Leavelle, 1955; Arnold, 1955; Oehring and Jütte, 1963; Walsh, 1965; McEntyre and Curran, 1968; Kurz and Weiss, 1969).

A further patient is now reported as this is the first documented case in which hyperbaric oxygen was used as an adjuvant to therapy.

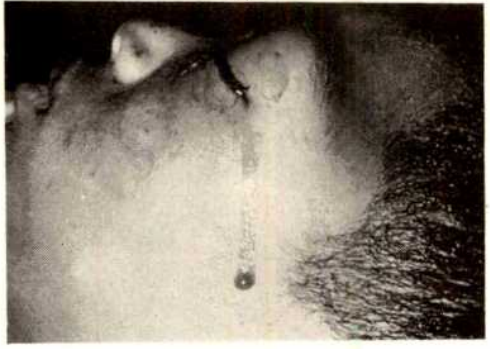
Case report

A 10-year-old boy came to the Eye Department of Groote Schuur Hospital on January 6, 1970, with a painful left eye. He had been making a fowl-run in a rather dirty and dusty back-yard 18 hours previously and, while hammering a nail, had suddenly experienced a sharp pain in the left eye. Immediately after the injury he had little pain, but that night the eye became painful, and within 12 hours there was swelling of the lids and a discharge from the eye.

Examination

The visual acuity of the left eye was only perception of light. There was severe lid oedema (Fig. 1) and conjunctival chemosis associated with some degree of global tenderness. A 4-mm. perforating wound in the cornea was covered by a brownish muco-pus (Fig. 2).

(1)



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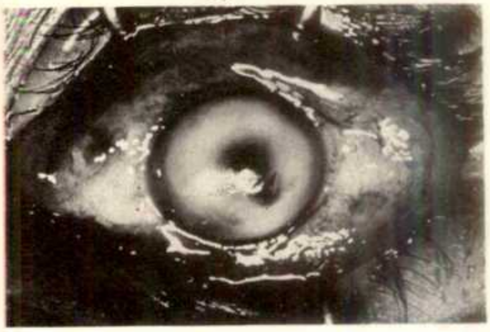

FIG. 1 *Swelling of periorbital region as well as over the temporal fossa region. A brownish muco-pus is trickling over the skin.*

FIG. 2 *A 4-mm. perforating wound of the cornea is covered by muco-pus.*

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The anterior chamber was shallow and the iris leaf was not clearly seen as it was obscured by hypopyon and gas bubbles. There was no red reflex on fundoscopy. Ocular movements were full in all directions of gaze. *X* ray of the orbits demonstrated a radio-opaque intraocular foreign body lying posteriorly in the globe (Fig. 3). While the swab was being taken for bacteriological examination a sweetish-smelling gas escaped from the corneal wound with an audible hiss.

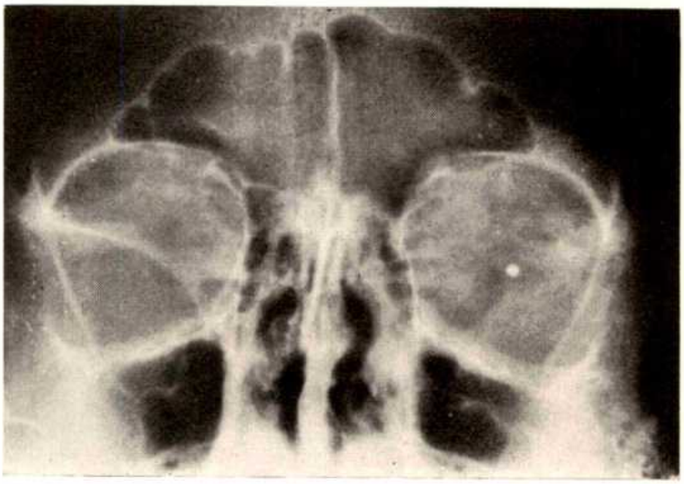

FIG. 3 *X ray of orbit, showing intraocular radio-opaque foreign body*

Bacteriological examination

The exudate showed scanty Gram-positive bacilli, morphologically compatible with a clostridial species (Fig. 4).

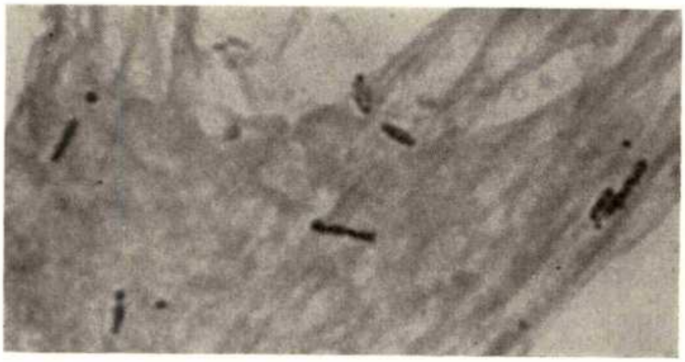

FIG. 4 *Rod-shaped* Clostridium welchii *bacilli. Gram stain.* × 700

On culture a scanty but pure growth of a Gram-positive bacillus was obtained with the following characteristics:

(1) Smooth rounded β-haemolytic colonies on horse-blood agar, growing only anaerobically.

(2) The production of a "stormy clot" in litmus milk medium.

(3) Inoculation of the organisms onto a lecithin-containing medium and anaerobic culture showed the presence of lecithinase activity, which was neutralized by *Clostridium welchii* alpha antitoxin.

In addition a growth of *Staphylococcus aureus* was obtained from another swab.

The right eye showed no pathology and the visual acuity was 6/6.

The child's general condition was unsatisfactory; he was drowsy and apathetic, the temperature was 102·2°F., and the pulse 102/min. Terminal neck stiffness was present. Lumbar puncture revealed a pressure of 120 mm. H^2O, the protein was 10 mg. per cent. and the glucose was within normal limits using the Dextrostix. The cerebrospinal fluid was clear and there were no cells on microscopical examination.

A full blood count showed haemoglobin 13·3 g. per cent., total white cell count 6,800 per cu. mm. (neutrophils 52 per cent., eosinophils 7 per cent., lymphocytes 33 per cent.).

Diagnosis

Gas gangrene panophthalmitis was diagnosed and therapy was immediately commenced.

Treatment

Intravenous penicillin 20,000,000 u per 1,000 ml. normal saline was administered over the first 24-hour period. In addition 1 ml. formol tetanus toxoid was given intramuscularly. Within 18 hours of starting therapy the patient's condition deteriorated. There was a marked increase in the lid swelling which extended laterally into the temporal fossa. The conjunctival chemosis increased considerably. The hypopyon level rose and the iris could not be seen. Although the temperature had dropped to 100°F. and the pulse rate to 100/min., the child was more apathetic and toxic. An Astrup examination revealed a satisfactory acid-base relationship: *viz.* ph. 7·42 base excess + 3·6. The urinary output during the first 20 hours of hospitalization was 900 ml.

In view of the ocular and systemic deterioration on antibiotic therapy alone, the patient was taken to the operating theatre and on January 7, 1970, the left eye was eviscerated. The globe contained necrotic tissue and haemolysed blood. No intraocular elements were recognizable macroscopically. A 2 × 3 mm. metallic foreign body was recovered from within the globe.

Because of the marked oedema of the orbital tissue, and the conspicuous swelling of the lids and temporal region, orbital and extraorbital extension of the gas gangrene was suspected, and on January 7, 1970, hyperbaric oxygen therapy was commenced. The patient was treated in a single-patient transparent hyperbaric oxygen chamber filled and ventilated with 100 per cent. oxygen at a pressure of 3 atmospheres absolute, *i.e.* 29·4 lb./sq. in. During the 30 hours after evisceration he spent six 2-hour periods in the oxygen chamber. The intravenous penicillin therapy was continued for 5 days postoperatively and from the first postoperative day 40 mg. gentamycin was given intramuscularly twice daily.

48 hours after starting the hyperbaric oxygen treatment, there was systemic improvement. The temperature and pulse rate settled to normal levels and the patient became alert and interested in his surroundings. By the 4th postoperative day the periorbital swelling and tenderness had completely subsided and there was minimal discharge from the socket.

Result

The subsequent course was uneventful and the patient was discharged on January 16, 1970. A prosthesis was fitted 6 weeks after the operation.

Discussion

Panophthalmitis following the entry of an intraocular foreign body is rarely complicated by gas gangrene. The distinctive characteristics of gas gangrene panophthalmitis are marked lid swelling, severe conjunctival chemosis, and a coffee-coloured discharge from the eye, the last being a constant finding. In addition, hypopyon and gas in the anterior chamber may be observed. Gas in the anterior chamber has not always been noted in the previous cases described. Numerous swabs should be taken and the laboratory specifically requested to look for *Clostridium welchii* bacilli.

In the previous cases described, the infection has been controlled by antibiotic therapy and either evisceration or enucleation. No eye with proven gas gangrene panophthalmitis has ever been saved by antibiotic therapy alone.

Leavelle (1955), in his review of 55 cases, reported two patients who required exenteration of the orbit. One of these had an enucleation as a primary procedure, but this failed to control the infection as there was evidence of extraocular spread of the infection. The other case required exenteration as a primary procedure.

Slack, Hanson, and Chew (1969) maintained that hyperbaric oxygen, by reducing toxaemia and arresting futher spread of the disease, re-established the state in which antibiotic therapy and debridement can once more be effective. Hyperbaric oxygen does not kill *Clostridium welchii* organisms, but inhibits their growth. It is doubtful whether hyperbaric oxygen has in fact any effect on the avascular cornea, lens, and vitreous. Furthermore, ocular blood vessels like those of the brain constrict in the presence of increased oxygen tension (Saltzman, Anderson, Hart, Duffy, and Sieker, 1965; Brummelkamp, 1965). Hyperbaric oxygen was used in this case because there was the possibility that the gas gangrene had extended beyond the eye to involve the orbital and surrounding tissue.

Intensive antibiotic therapy with evisceration or enucleation is the treatment of choice with gas gangrene panophthalmitis. Hyperbaric oxygen is indicated only when there is clinical evidence of extraocular extension of the gas gangrene.

The bacteriological examination was carried out by Dr. A. Forder of the Department of Bacteriology, Groote Schuur Hospital.

The investigation was financed by the Gratitude Fund of Ophthalmology and the Goosen Fund, University of Cape Town.

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Book reviews

So You Have Glaucoma. By E. R. VEIRS. 2nd ed., 1970. Pp. 84, 14 figs. Grune & Stratton, New York and London. ($5.75)

An account of glaucoma for the lay public. The book consists of an historical section, an account of ocular anatomy and physiology as they affect glaucoma, accounts of the incidence and pathology of the disease, and a description of congenital glaucoma. There follows a section on the signs and symptoms and diagnosis and finally a description of treatment. In a postscript the patient is encouraged that if he follows his prescribed treatment faithfully he is very unlikely to go blind.

It is difficult for a medical reviewer to put himself in the position of the lay public; the problem is one of altering one's own level of comprehension to fit that of a person with no knowledge of medical jargon or of small-scale anatomy and of physiology. On the whole the author has done very well in this, the most important aspect of a book of this type.

Contact Lens Medical Seminar. Vol. 1. Edited by W. G. SAMPSON and G. L. FELDMAN. 1970. Pp. 168, refs. Thomas, Springfield, Ill. ($10.50)

The publication in stiff-backed book form of a small collection of papers read at international meetings is now considered an accepted necessity, but to extend this to small seminars (including panel discussions) is a development which causes this reviewer some alarm. This trend is occurring at a time when the number of seminars and the cost of producing books are increasing rapidly. Publishers must routinely print original matter, subjects that require up-dating or re-appraisal, basic texts that provide a guide for the undergraduate or post-graduate student, but since contact lens practice is undergoing such rapid changes one wonders whether a book in this form is necessary.

The present volume contains eleven papers all documented elsewhere, but with some small additional material added mostly in the form of editorial notes. It is 2 years since the seminar was held. The value of this text must, therefore, be limited. There is, however, fun in this book for those who know the personalities of the panel participators. The reviewer was delighted by the innuendoes and laughs up the sleeve that can be read into the questions and answers. Some are directed with the consummate skill of a harpoonist. To the student of contact lens practice this slim volume will provide light reading if he is unfamiliar with the high standard of contact lens practice among specialist ophthalmologists in the U.S.A. One commends W. G. Sampson for his depth of understanding of the optics applied to contact lens design and fitting.

The Conservative Management of Squint. By W. AUST, translated into English by C. H. BEDWELL and H. OBSTFELD from a revised and enlarged version of "Pleoptik und Orthoptik". 1970. Pp. 150, 69 figs, bibl. Karger, Basel. (46*s.*)

This book is based upon Aust's "Pleoptics and Orthoptics" originally published in German, and gives a full and detailed account of the author's methods and investigations and treatment of squint. Following a classification of the types of squint and notes on diplopia, the author presents a comprehensive account of the sequence of investigations and explains how to perform the tests that will lead to a diagnosis. Sections on the use of the Visuscope to characterise fixation, and ways of assessing retinal correspondence, are particularly full; 21 pages are devoted to investigations with the synoptophore before coming to the treatment section which comprises occlusion therapy and pleoptic training by the methods of Cüppers (17 pages) and Bangerter (4 pages). The final section deals with orthoptic exercises.

The translation is stilted at times, and some curious words have emerged: "trochleatis" for "superior oblique", "compulsory" head posture, "folding" instead of "tucking" a muscle, "resectioned" for "resected", and "tweezers" for "forceps".

Perhaps the most disappointing feature of this book is the complete omission of any facts about results. Surely the reader is entitled to at least a table showing the number of patients who have benefited from the treatment, particularly the pleoptic treatment, so that a realistic prognosis could be given to parents (and child) about the success rate of this time-consuming therapy. On page 100 it is stated: "*After years of occlusion treatment* (reviewer's italics), we see in more children a normal correspondence".

Despite these criticisms the book gives a useful description of the techniques used in squint management in Marburg. Although it will prove mainly of value to orthoptists it is certainly worthwhile reading for ophthalmologists who are interested in the difficult problem of binocular cooperation.

BOOKS RECEIVED

Transactions of the Asia-Pacific Academy of Ophthalmology. Vol. 3. Third Congress, Singapore, 1968. Edited by R. C. K. Loh and G. L. Voon. 1970. Pp. 556, figs, refs. Printers and Converters (Ptc) Ltd., Singapore.

Notes

Massachusetts Eye and Ear Infirmary

Course in Retinal Detachment, June, 1971

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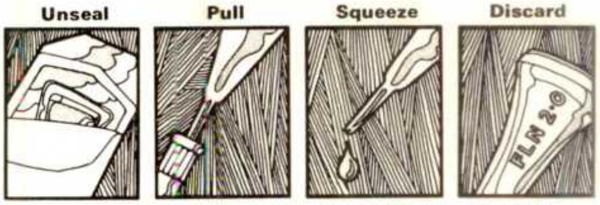

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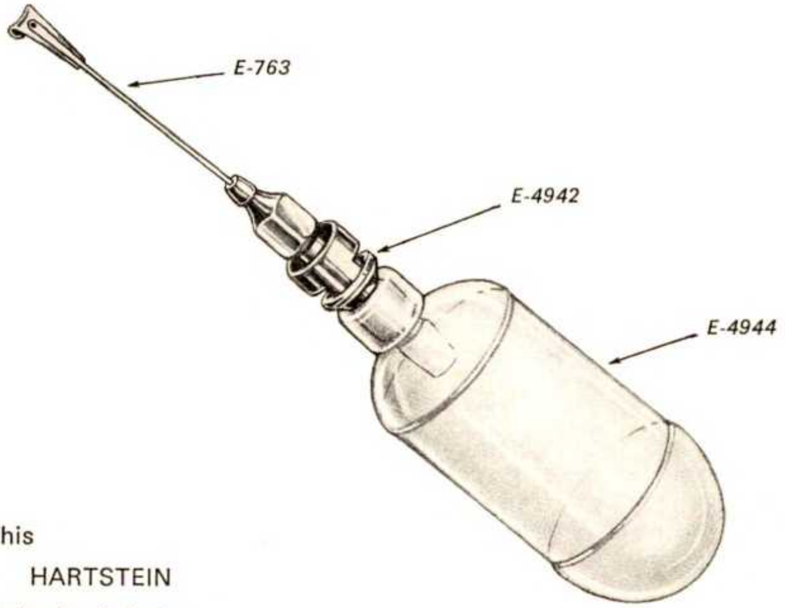

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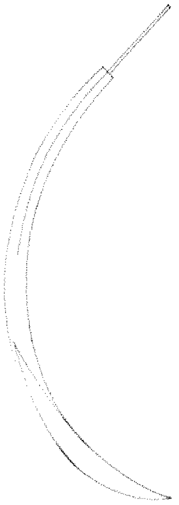

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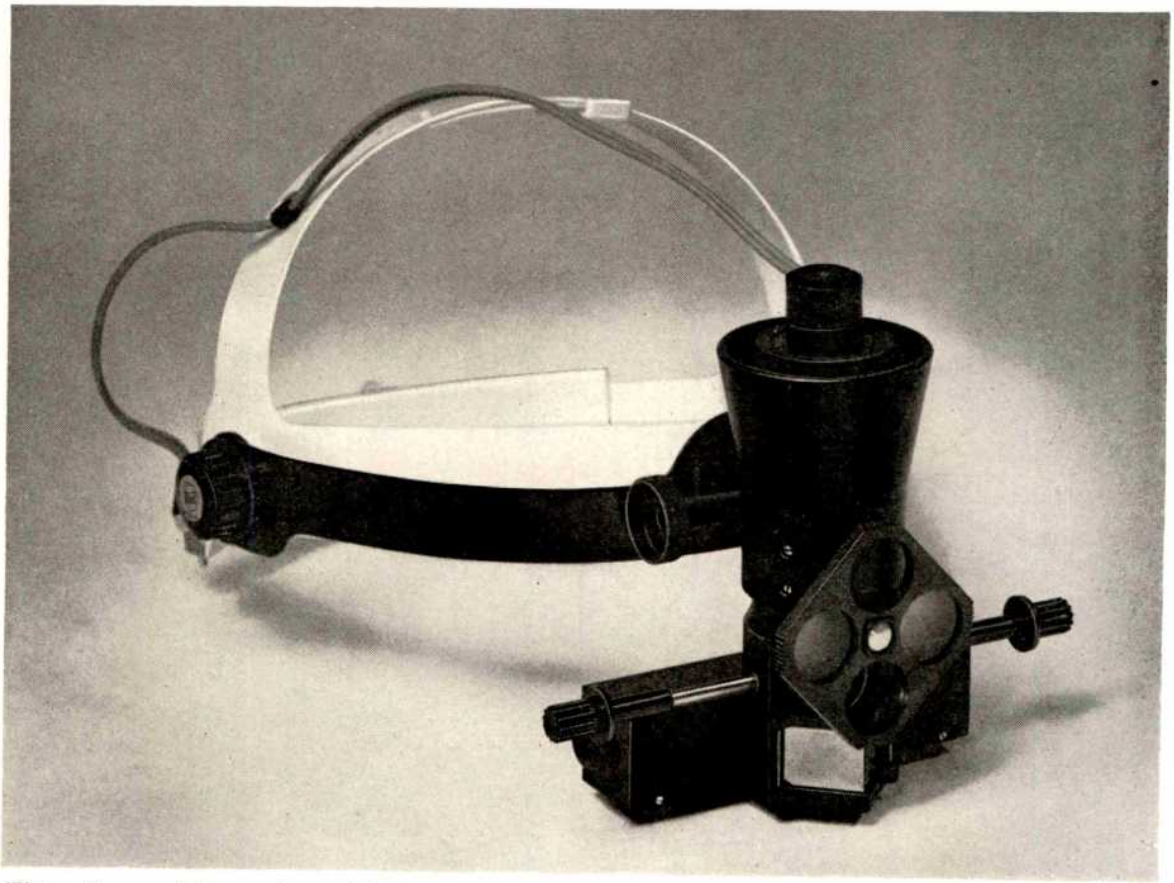

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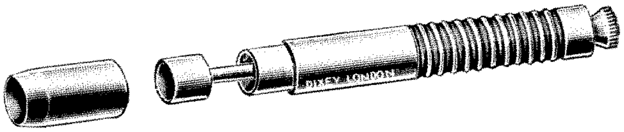

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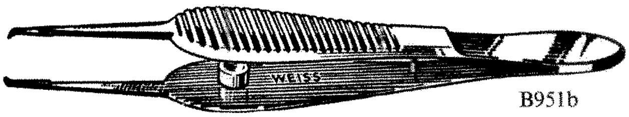

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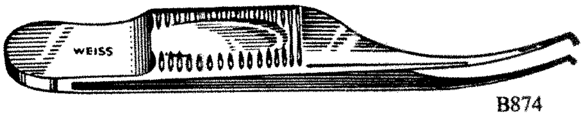

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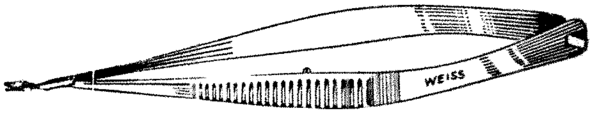

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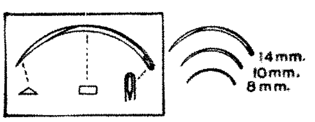

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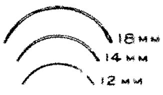

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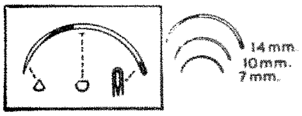

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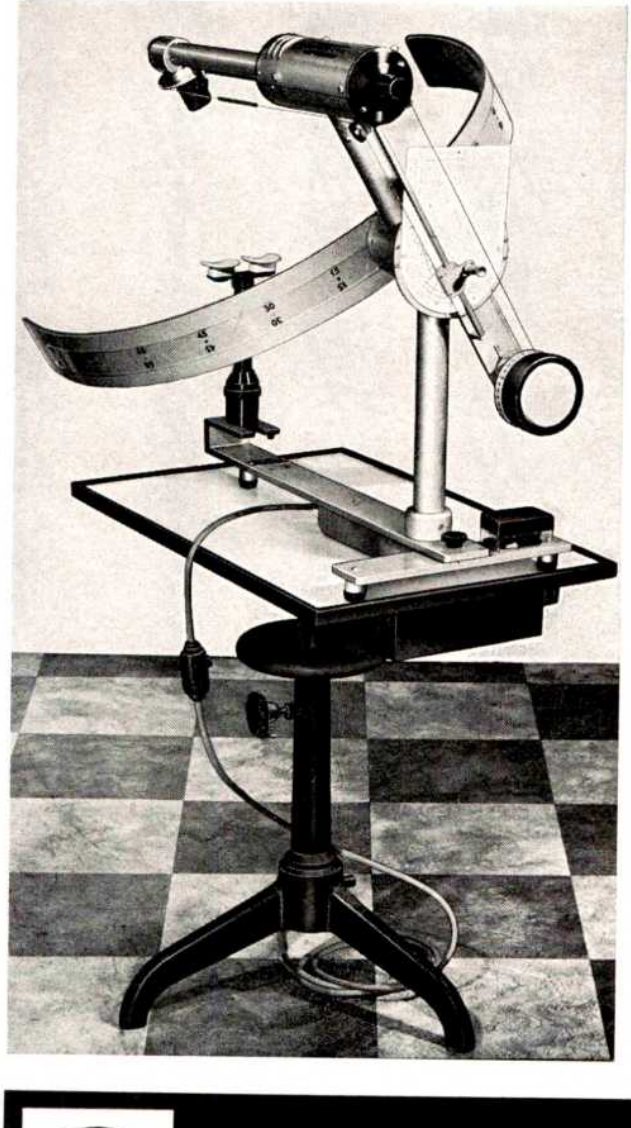

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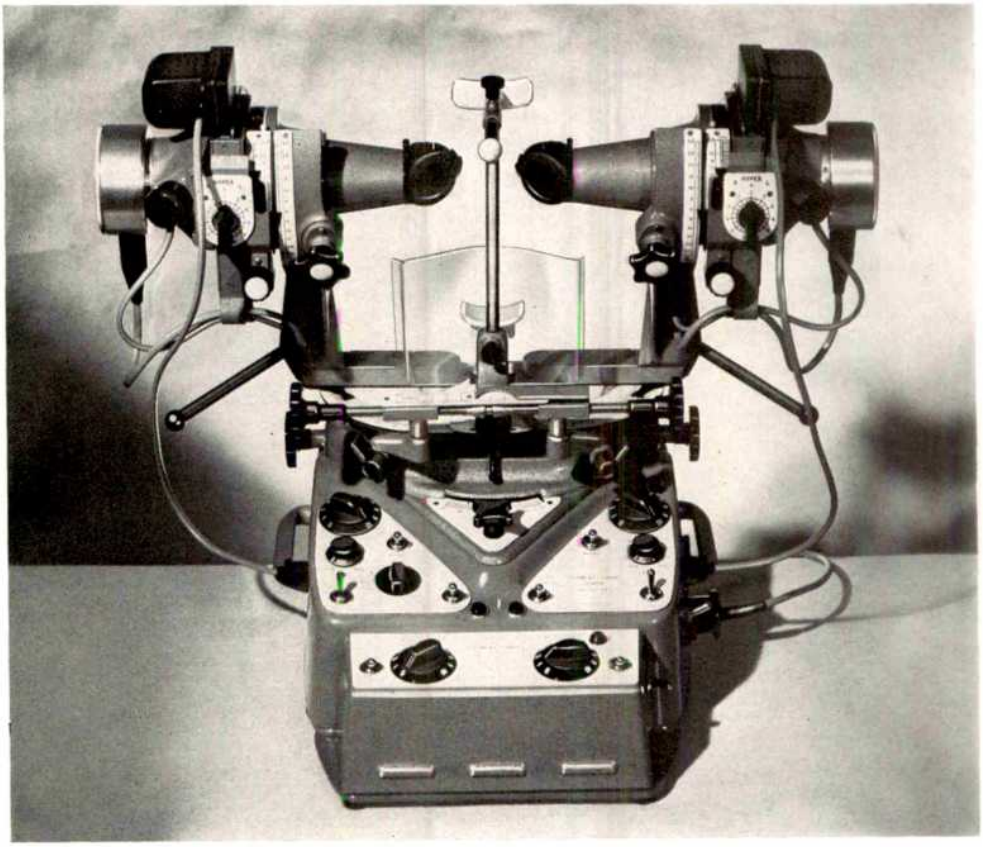

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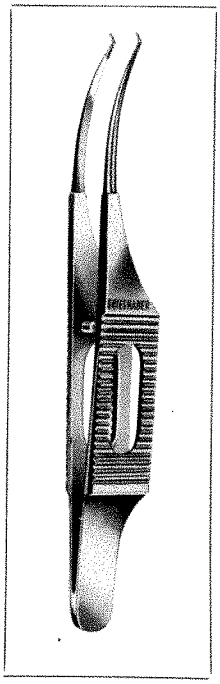

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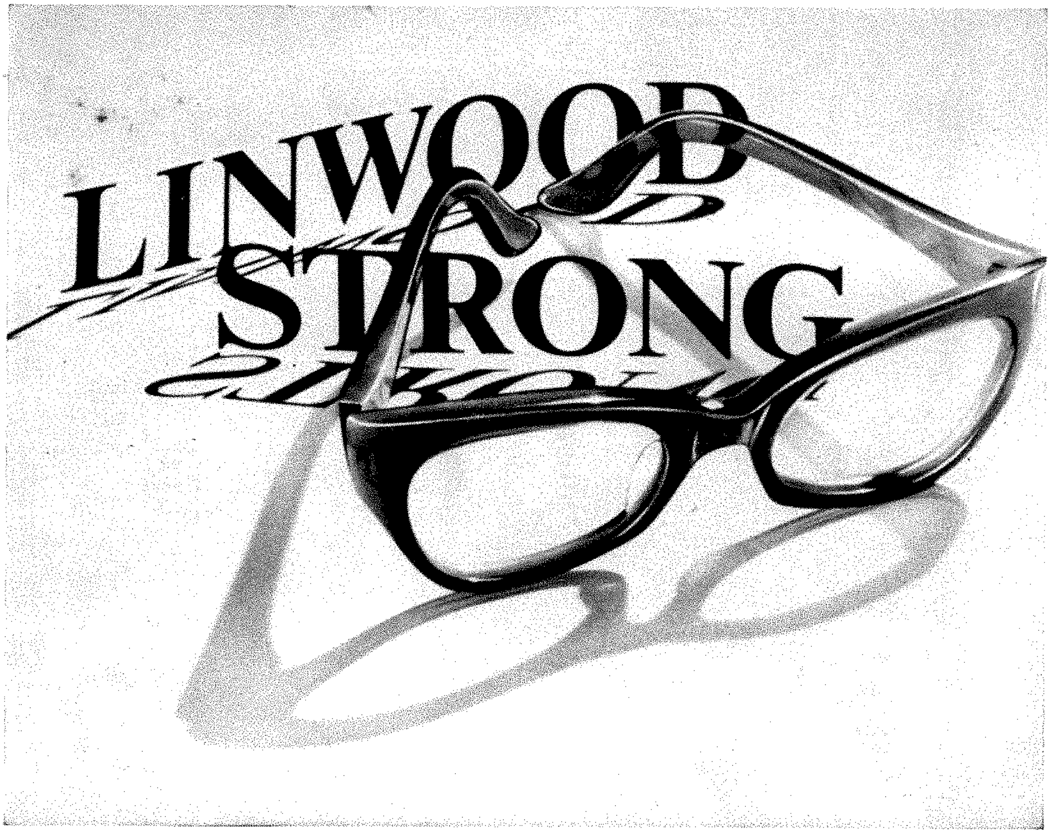

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Communications

Clinical aspects of oculo-auriculo-vertebral dysplasia

D. I. BOWEN, L. M. T. COLLUM, AND D. O. REES

Cardiff Royal Infirmary

Oculo-auriculo-vertebral dysplasia is a condition characterized by epibulbar dermoids or dermolipomata, auricular deformities, and vertebral anomalies. Many other abnormalities have been described, but these three signs are the most constant and give the syndrome its identity. In this communication we are presenting four further cases each of which demonstrates additional clinical and radiological features.

Case reports

Case 1, a 16-month-old boy was admitted to hospital for the removal of a dermolipoma from his left eye. This had been noted soon after birth, but surgery had been deferred.

He had a right indirect inguinal hernia repaired at the age of 3 months and he had had apparent difficulty in swallowing throughout his first year, but a barium swallow had been normal.

EXAMINATION

A dermolipoma was situated on the lower temporal quadrant of the left globe encroaching onto the cornea. This appeared to have increased in size since it was first observed 12 days after birth. A similar but smaller tumour was noted in the lower temporal region of the right eye several millimetres posterior to the limbus adjacent to the conjunctival fornix.

GENERAL EXAMINATION

(1) Hypoplasia of the left side of the face.

(2) Deformed left pinna.

(3) Blind left external auditory meatus which was represented by a small pit only.

(4) Abnormal left thumb, with the phalanges apparently connected to the rest of the hand by soft tissue only (Fig. 1, overleaf).

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(1) *Multiple vertebral and costal anomalies* Spina bifida occulta of cervical and upper thoracic vertebrae; fusion of a cervical rib with right first rib and fusion of a hypoplastic left first rib with the second; fusion of body of T4 with left half of T5; hemivertebrae at T5 and at the thoraco-lumbar junction.

(2) *Anomalies of facial bones* Hypertelorism; hypoplasia of left mandibular ramus.

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(3) *Temporal bone anomalies* Atresia of left external auditory canal; elevation of left cochlea producing asymmetry of the petrous temporal bones; underdevelopment of mastoids.

(4) *Abnormal left thumb* The digit arose distally and had three hyperplastic bones with the configuration of phalanges; the metacarpal bone was absent.

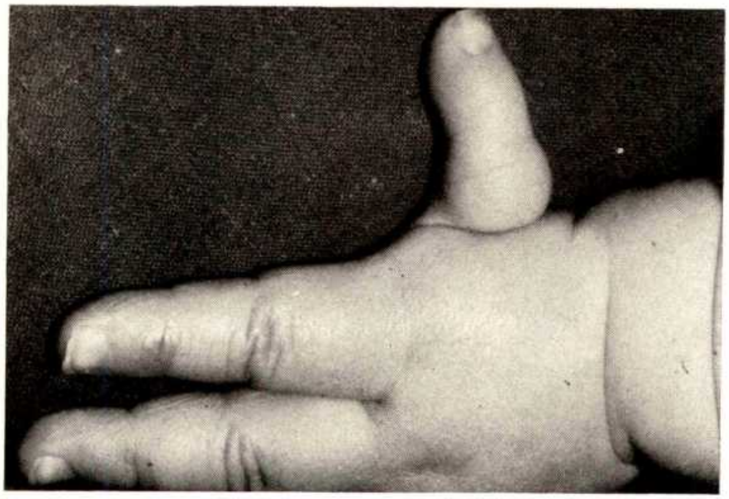


FIG. 1 *Case* 1. *Abnormal left thumb*

COURSE

The left dermolipoma was removed under general anaesthesia. It was closely adherent to the underlying sclera and cornea and after dissection the exposed corneal stroma was left bare. The excised specimen consisted of a soft mass with a number of hairs projecting from its surface and histological examination showed that it was composed of adipose tissue. After the operation a purulent discharge developed and pressure on the lacrimal sac resulted in regurgitation of pus, from which *D. pneumoniae* were cultured. The left nasolacrimal duct was probed and the discharge cleared within a few days. A month later, however, the eye had become re-infected and a central corneal ulcer had developed. Corneal sensation at this time was shown to be absent. A further probing again reduced the amount of discharge, but the ulcer persisted and for 6 weeks remained unchanged. Finally it was decided that the diseased cornea should be replaced by a graft, and, in order to prevent further re-infection from the lacrimal sac, a dacryocystectomy was done as a preliminary procedure. After a further 4 weeks, when the child was aged 19 months, a 5·1 mm. central penetrating corneal graft was performed. The post-operative course was uneventful, there was no further infection, and the graft has remained clear (Fig. 2).

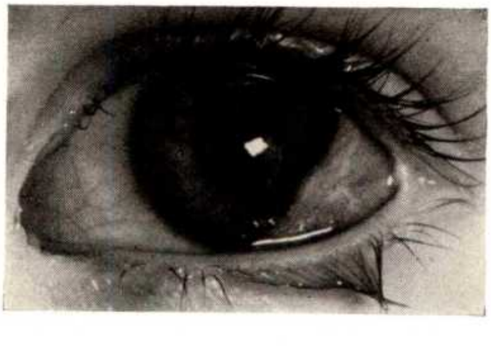


FIG. 2 *Case* 1. *Appearance of graft in left eye* 10 *months after surgery*

COMMENT

This is a typical case of oculo-auriculo-vertebral dysplasia, showing as it does the characteristic triad of signs. The complications arising after the excision of the left dermolipoma can be directly attributed to corneal anaesthesia and obstruction of the nasolacrimal duct. Sugar (1967) has reported the absence of corneal sensation in this syndrome but we have found no references to nasolacrimal duct obstruction. We believe also that this is the first report of a penetrating corneal graft done in a patient with this syndrome, although lamellar grafts have been described (Sugar, 1966; Heimann, 1968).

Case 2, a girl aged 6 years, was seen in the Eye Clinic in January, 1970, for advice about her right eye which periodically became red and painful. The trouble had been present since the age of 11 months at which time a tarsorrhaphy had been done; this had broken almost immediately.

EXAMINATION

The right eye showed a central corneal scar with some vascularization (Fig. 3) and the visual acuity was hand movements only. There was total corneal anaesthesia and a dermolipoma was present at the limbus in the lower temporal quadrant (Fig. 3). The left eye was normal with a visual acuity of 6/4. The nasolacrimal ducts were freely patent to syringing.

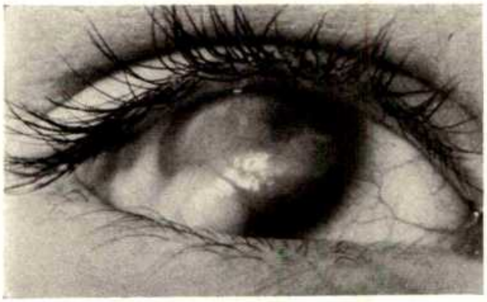


FIG. 3 *Case 2. Appearance of right eye, showing corneal scarring and dermolipoma*

GENERAL EXAMINATION

(1) Hypoplasia of the right side of the face (Fig. 4, overleaf).

(2) Deformed right pinna (Fig. 5, overleaf).

(3) The remains of preauricular skin tags which had been removed in the past.

(4) Blind right external auditory meatus.

(5) Abnormally mobile interphalangeal joint of the right thumb.

(6) Bilateral pes planus.

(7) Bifid uvula.

(8) Peculiar gait. This was the result of hip abnormalities for which she had had plates inserted at the age of 4 years. These have just recently been removed.

RADIOLOGICAL EXAMINATION

(1) *Multiple vertebral and costal anomalies* Hemivertebra at T5 and cuneiform vertebrae at T2 and T3; atresia of right first rib and fusion of right second and third ribs; spina bifida occulta of cervical vertebrae.

(2) *Anomalies of skull and facial bones* Biparietal foramina; abnormally small pituitary fossa; hypoplasia of right maxilla including the antrum; hypoplasia of right side of mandible.

(3) *Right temporal bone anomalies* Atresia of external auditory canal; absence of ossicles; malformed elevated cochlea; short hypoplastic external auditory canal with acute upward inclination; underdeveloped diploic mastoid.

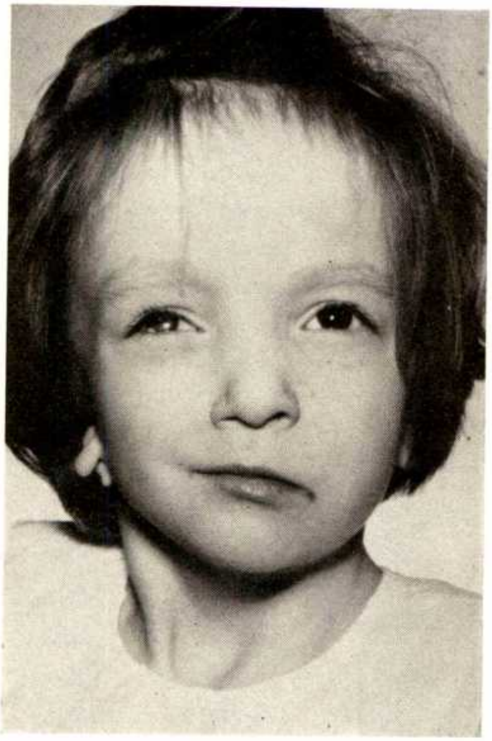


FIG. 4 *Case 2. Full face, showing right hypoplasia*

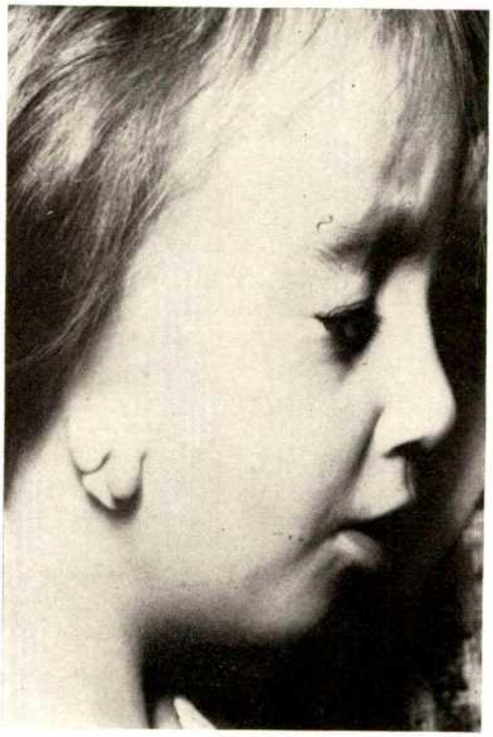


FIG. 5 *Case 2. Side face, showing deformed right pinna*

COMMENT

This patient also presents a typical case of oculo-auriculo-vertebral dysplasia. The bifid uvula is an unusual feature but has been previously reported (Neimann, Cordier, Manciaux, and Barrucand, 1960). The extensive corneal scarring was almost certainly related to the absence of corneal sensation. As the eye was likely to be amblyopic and there was no active ulceration, keratoplasty was not advised.

Case 3, an infant girl aged 1 month, was seen in 1963 because she apparently had only one eye. She was examined under general anaesthesia and indeed there was no evidence of an eye on the left side (Fig. 6); the socket was empty and the bony orbit was only half the normal size. The right eye was normal apart from a limbal dermoid (Fig. 6). When we reviewed her recently at the age of 8 years, we found no change in her ocular state but we noted in addition that her corneal sensation was much reduced. Her mother told us that she had a recurring discharge from her right eye but that this gave her little trouble. A sac wash-out was not done.

GENERAL EXAMINATION

(1) Hypoplasia of the right side of mandible (Fig. 6, opposite).

(2) Preauricular skin appendages.

(3) Cleft palate. This had been treated surgically when she was 2 years old.

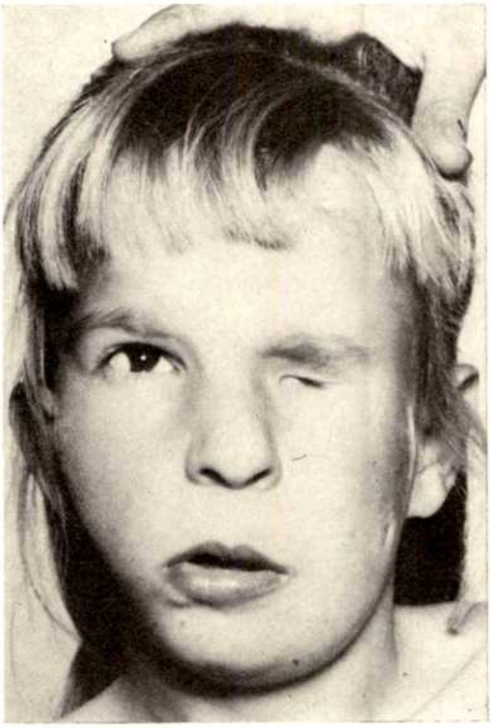
(4) Scoliosis (Fig. 7, opposite).

(5) Paralytic equino-varus of left foot. This has been under treatment since the age of one month.

(6) Short atrophic left lower limb below knee level (Fig. 8, opposite).

(7) Imperforate anus with recto-vaginal fistula.

(6)



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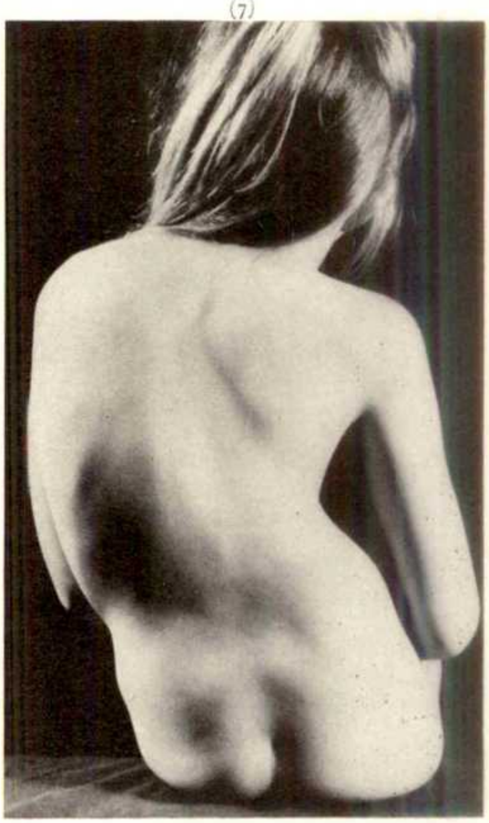

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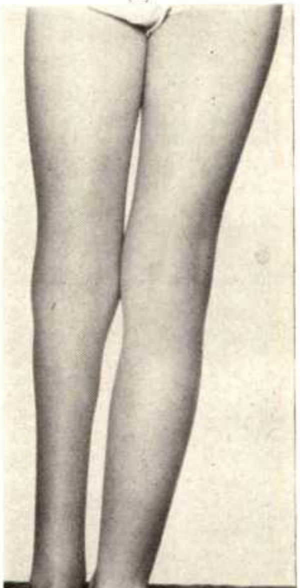


FIG. 6 *Case* 3. *Full face, showing absence of left eye, right limbal dermoid, and facial asymmetry*

FIG. 7 *Case* 3. *Back, showing scolosis*

FIG. 8 *Case* 3. *Short atrophic left lower limb*

RADIOLOGICAL EXAMINATION

(1) *Multiple vertebral anomalies* Failure of segmentation resulting in block vertebrae throughout the thoracic and lumbar spines; fusion of the right lower eight ribs; cuneiform and hemivertebrae.

(2) *Anomalies of skull and facial bones* Biparietal foramina; an abnormally small pituitary fossa; hypoplasia of the left orbit and left side of mandible; aplasia of the right mandibular ramus.

(3) *Temporal bone anomalies* Hypoplasia of the bony external auditory canals; absence of the ossicles on the left; hypoplastic internal auditory canals and a malformed elevated cochlea on the right underdeveloped mastoids.

(4) *Right-sided hydronephrosis and hydroureter* (IVP)

COMMENT

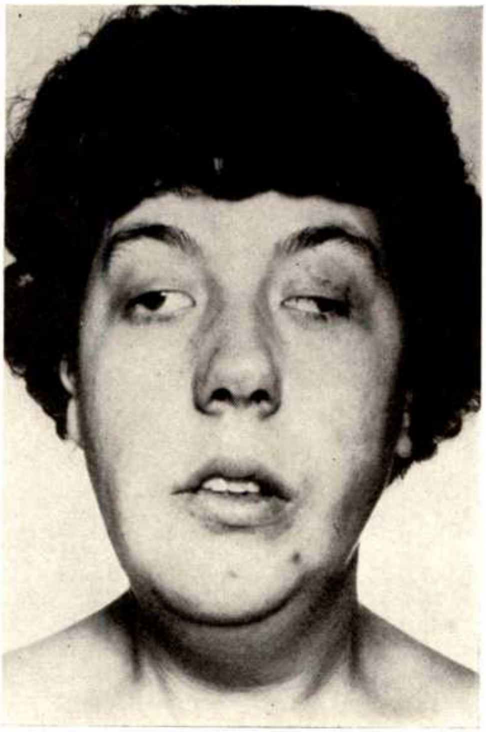
This girl has all the features of oculo-auriculo-vertebral dysplasia as well as a large number of additional anomalies. The feature of corneal anaesthesia is again noted here but in this case there has never been any corneal ulceration.

Case 4, a woman aged 29 years, was referred to the Eye Clinic for advice about her ptosis. She was deaf and dumb but her sister, who used sign language, was able to communicate with her without difficulty. She had had a series of operations on her ears at the age of 13 but there had been no improvement in her hearing. Her eyes had been abnormal since birth and a ptosis operation was performed on the left side at the age of 5.

EXAMINATION

There was a gross divergent squint, bilateral ophthalmoplegia, and marked bilateral ptosis with scarring of the left upper lid (Fig. 9). In the left eye abduction was full and some depression was possible, but elevation and adduction were absent. In the right eye partial abduction was the only movement elicited. She adopted an abnormal head posture to compensate for her ptosis and

(9)



(10)

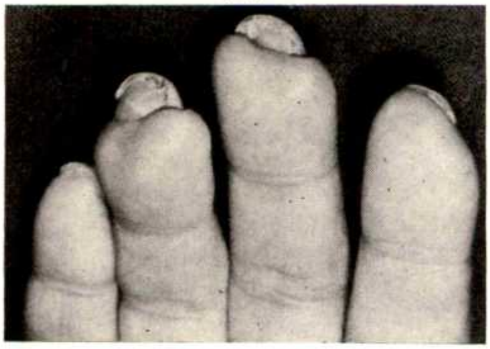


FIG. 10 *Case 4. Fingers, showing hypoplasia of terminal phlanges*

FIG. 9 *Case 4. Full face, showing ptosis and squint*

ophthalmoplegia. She had no diplopia. The corrected visual acuity was 6/9 in the right eye and 6/12 in the left. The fundi were normal. There was a lobulated epibulbar dermolipoma a few millimetres to the lateral side of the limbus on the right eye. Corneal sensation was normal on both sides and the naso-lacrimal ducts were patent on syringing.

GENERAL EXAMINATION:

(1) Deformed right pinna.

(2) Blind external auditory meati on both sides.

(3) Hypoplasia of terminal phalanges on several fingers and toes (Fig. 10).

RADIOLOGICAL EXAMINATION

(1) *Vertebral anomalies* Abnormally high vertebral bodies with narrow disc spaces and marked osteophyte formation; narrow spinal canal.

(2) *Skull anomalies* Patchy hyperostosis of frontal bones; abnormally small pituitary fossa.

(3) *Temporal bone anomalies* Bilateral atresia of external auditory canals; bilateral absence of ossicles; underdeveloped mastoids.

(4) *Hand abnormalities* Hypoplasia of third, fourth, and fifth terminal phalanges of both hands.

COURSE

Under general anaesthesia the dermolipoma was removed and the right lateral rectus recessed 8 mm. Histological examination of the excised specimen showed that it consisted largely of adipose tissue. Post-operatively a purulent conjunctivitis developed with a marginal ulcer adjacent to the site of excision of the dermolipoma. The condition resolved in a few days with the administration of topical antibiotics. The effect of the squint surgery was disappointing and the cosmetic improvement slight. The patient is soon to be fitted with a shelved contact lens to assist the ptosis.

COMMENT

Although the ophthalmoplegia and ptosis are the most striking features of this case, we believe it may be classified as oculo-auriculo-vertebral dysplasia since it shows the association of an epibulbar dermolipoma, auricular abnormalities, and spinal changes. As in Case 1 a corneal ulcer developed after the excision of the dermolipoma. It resolved rapidly but if corneal anaesthesia or naso-lacrimal duct obstruction had been present the course may well have been more protracted. The absence of discrete middle ear ossicles was demonstrated by tomography of the petrous temporal bones. Unfortunately we have been unable to obtain any records relating to the operations performed on the patient's ears so we cannot say with any certainty whether this anomaly is congenital or the result of surgery.

Discussion

Goldenhar (1952) drew attention to the association of epibulbar dermoids, auricular appendages, and blind fistulae in the preauricular area, and his name has since become associated with this particular syndrome. The vertebral anomalies often found in Goldenhar's syndrome were not reported until later (Gorlin, Jue, Jacobsen, and Goldschmidt, 1963; Sugar, 1967; Berkman and Feingold, 1968) and the condition has now become known as oculo-auriculo-vertebral dysplasia. Two other conditions which may cause confusion are:

(1) Oculo-vertebral dysplasia (Weyers and Thier, 1958), which is characterized by unilateral mandibulo-facial dysostosis, malformation of the globe, and developmental anomalies in the vertebral column;

(2) Cervico-oculo-acoustic dysplasia (Wildervanck, 1960), which has as its main features the Klippel-Feil syndrome, congenital ocular muscle anomalies, and deaf-mutism. These conditions are separate entities and can be differentiated from the syndrome in question.

The typical ocular findings in oculo-auriculo-vertebral dysplasia are epibulbar dermoids or dermolipomata. These are milky white or yellow in colour and soft in consistency and are usually situated at the limbus where they may encroach onto the cornea. Histological examination of these lesions in two cases showed a preponderance of adipose tissue. The characteristic auricular abnormalities are hypoplasia and deformity of the

Table *Additional anomalies in oculo-auriculo-vertebral dysplasia*

Ocular	*Facial*	*Oral*
Lid colobomata	Unilateral facial hypoplasia	Macrostomia
Ptosis	Receding chin and mild malar hypoplasia giving a parrot-like appearance	Enlarged philtrum
Nasolacrimal obstruction	Nostril atresia	Micrognathia
Ophthalmoplegia	Displaced nasal septum	Aplasia of ramus and condyle of mandible
Squint	Fibrous band from angle of mouth to tragus	High-arched palate
Duane's retraction syndrome	Abnormal eyebrow	Bifid tongue
Exophthalmos	Mandibulofacial dysostosis	Bifid uvula
Corneal anaesthesia	Oculo-vertebral syndrome	Double lingual frenum
Corneal ulceration		Cleft palate
Persistent pupillary membrane		Malocclusion of teeth
Iris atrophy		Dental malformations
Polar cataract		
Uveal colobomata		
Microphthalmia		
Anophthalmos		

Cranial	*Musculo-Skeletal*	*Miscellaneous*
Biparietal foramina	Occipitalization of the atlas	Deaf-mutism
Open anterior fontanelle	Hemivertebrae in any position	*Cri-du-chat* syndrome
Accentuated frontal suture	Cuneiform vertebrae	Tetralogy of Fallot
Frontal bossing of skull	High vertebral bodies	Bundle branch block
Hypertelorism	Narrow disc spaces	Inguinal hernia
Hypoplasia of orbit	Complete or partial synostosis of two or more vertebrae	Mild mental defect
Low hair line	Supernumerary thoracic or lumbar vertebrae	Epilepsy
Petrous temporal anomalies	Narrow spinal canal	Umbilical hernia
Small pituitary fossa	Anomalous ribs	Hydronephrosis and hydroureter
	Hip abnormalities	Imperforate anus
	Spina bifida	Rectovaginal fistula
	Scoliosis	
	Lumbaralization of S1	
	Sacral vertebrae aplasia	
	Sacral fovea	
	Limb and digit anomalies	
	Equino varus	
	Pes planus	

pinnae of the ears, blind or absent external auditory meati, bilateral preauricular skin appendages, and blind fistulae in the preauricular area. The commonest vertebral anomalies are cuneiform vertebrae, hemivertebrae, complete or partial synostosis of two or more vertebrae, and spina bifida.

The many associated anomalies, including our new findings, are summarized in the Table (Goldenhar, 1952; Paufique, Etienne, and Moreau, 1952; Kühnel and Dominik, 1954; Vannas, 1955; Cordier, Dureux, and Barrucand, 1961; Wille-Jørgensen, 1962; Gorlin and Pindborg, 1964; Joannidis and Protonotarios, 1964; Manfredini and Manuelli, 1964; Smithells, 1964; Brancato and Artifoni, 1965; Sugar, 1966, 1967; Slem, 1967; Ladekarl, 1968; Mortada, 1969; Pieroni, 1969). The four cases described in this paper illustrate well the variety of signs which can appear in these patients. The abnormal radiological signs are particularly abundant and include features that have not been described previously. For instance, asymmetry of the petrous temporal bones has been noted by Darling, Feingold, and Berkman (1968), but by the employment of a polytomographic apparatus we have been able to add to this observation by demonstrating the underlying anomalies of the structures of the internal ear. These radiological features will be described in greater detail in another communication (Rees, Collum, and Bowen, 1971).

The particular ocular feature to which we wish to draw attention is corneal anaesthesia. In Cases 1 and 2 corneal sensation was completely absent and in Case 3 it was grossly reduced. In Case 1 there was an associated obstruction of the naso-lacrimal duct on one side and a corneal ulcer developed after the excision of a dermolipoma. This ulcer became so resistant to conservative treatment that a therapeutic penetrating corneal graft was neccessary. Case 2 had extensive corneal scarring in one eye and a history of recurrent ulceration. Case 3 had reduced corneal sensation but no ulceration. Normally the excision of a limbal dermoid would be a straightforward procedure, although it might require a lamellar graft (Sugar, 1966; Heimann, 1968). The post-operative complications arising in Case 1, however, show that surgery in these patients should be undertaken with some caution. In Case 3, for instance, the limbal dermoid involves the patient's only eye and, although it is a cosmetic blemish, the risk involved contra-indicates surgery.

Case 4 presented with an ophthalmoplegia and ptosis, which we do not believe have been previously reported in association with oculo-auriculo-vertebral dysplasia. Both signs were said to have been present at birth and to have since remained static. This lack of progression and the absence of any other muscle weakness probably excludes a diagnosis of chronic progressive external ophthalmoplegia.

Summary

Four cases of oculo-auriculo-vertebral dysplasia are presented. New clinical and radiological features are described and the management of corneal complications is discussed.

We wish to thank Mr. M. V. Graham, Mr. P. A. Graham, Mr. P. V. Mills, and Mr. S. Pillai for allowing us to study their cases, and Miss Gail Ferguson for secretarial help.

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Superior oblique tendon sheath syndrome

An electromyographical study

G. V. CATFORD AND J. C. DEAN HART

London

The superior oblique tendon sheath syndrome was first described by Brown (1950), who noted that many cases of apparent congenital paresis of the inferior oblique muscle had restricted elevation in adduction on passive duction testing. At operation he observed thickening of the anterior part of the superior oblique tendon sheath, and when this was stripped away a full range of passive movements was possible.

Several reports have since appeared in the literature confirming these initial findings (Nutt, 1955; Girard, 1956; Folk, 1957; Esterly, Nadbath, and Russell, 1960). Spontaneous recovery was recorded by Costenbader and Albert (1958) and Lowe (1969). Impeded elevation in adduction was found to be associated in some cases with an audible click by Mein (1964) and Sandford-Smith (1969), who suggested local thickening of the superior oblique tendon as the causative factor.

Electromyography of the inferior oblique muscles in this syndrome revealed normal firing patterns (Breinin, 1957), but a further investigation of both oblique muscles of the affected side showed discharges indicative of an innervation disorder (Stein and Papst, 1968). Because of these conflicting opinions concerning the aetiology of this condition the authors carried out electromyography (EMG) on three adult patients with the superior oblique tendon sheath syndrome, and the results are reported below.

Method

Repeated instillation of Amethocaine 1 per cent. into the conjunctival sac ensured adequate surface anaesthesia.

Fine concentric needle electrodes were introduced into the superior and inferior oblique muscles through the upper and lower lids respectively, precise placement being confirmed by audio-amplification of the electrical activity from the muscles on attempted up and down gaze in adduction.

Insertion of the needle into the muscle belly of the superior oblique presented no difficulty if the trochlea was palpated and the needle was firmly advanced directly backwards, immediately medial to this structure.

The electrical activity from the muscles was displayed on a cathode ray oscilliscope after suitable amplification and was recorded photographically.

Case reports

Case 1, a 67-year-old woman, complained of steadily progressive vertical diplopia which was first noted at the age of 20. She had been treated with vertical prisms of increasing strength and was eventually unable to wear her prescription because of its excessive weight. There was no history of facial trauma.

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Examination

VISUAL ACUITY

6/9 in the right eye and 6/6 in the left.

OCULAR MOTILITY

Limited elevation of the left eye in adduction (See Hess chart, Fig. 1).

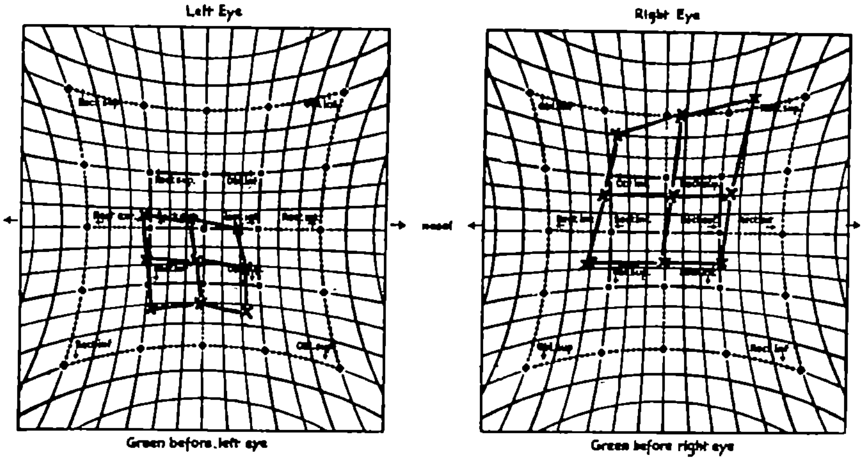

FIG. 1 *Case* 1. *Hess chart. Pseudoparesis of left inferior oblique. Overaction of right superior rectus.*

PASSIVE DUCTION TEST

Elevation in adduction markedly restricted in the left eye.

Diagnosis

Left superior oblique tendon sheath syndrome.

EMG

Normal firing patterns were recorded from the oblique muscles in the contracted and relaxed state (Figs 2 and 3).

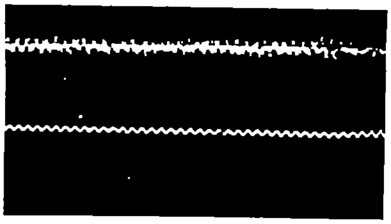

FIG. 2 *Case* 1. *Electromyograph of left superior oblique*

Upper trace: Attempted elevation in adduction (*relaxed*)

Lower trace: Depression in adduction (*contracted*)

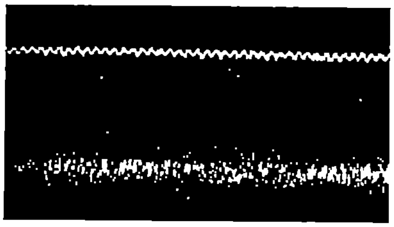

FIG. 3 *Case* 1. *E.M.G., left inferior oblique*

Upper trace: Depression in adduction (*relaxed*)

Lower trace: Attempted elevation in abduction (*contracted*)

Case 2, a 19-year-old man, had noted vertical diplopia 2 weeks after being involved in a minor traffic accident which had occurred 4 months previously. He gave no history of head injury or facial trauma.

Examination

VISUAL ACUITY

6/5 in each eye.

OCULAR MOTILITY

Limited elevation of the left eye in adduction (See Hess chart, Fig. 4).

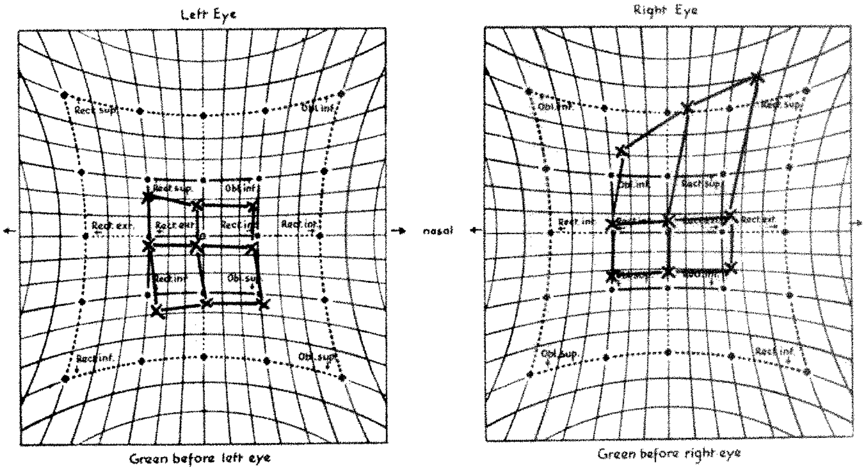

FIG. 4 *Case 2. Hess chart. Pseudoparesis of left inferior oblique. Overaction of right superior rectus.*

PASSIVE DUCTION TEST

Elevation in adduction restricted in left eye.

Diagnosis

Left superior oblique tendon sheath syndrome.

EMG

Normal firing patterns recorded from the left oblique muscles in the contracted and relaxed state (See Figs 5 and 6).

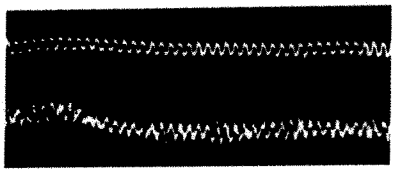

FIG. 5 *Case 2. E.M.G., left superior oblique*

Upper trace: Attempted elevation in adduction (*relaxed*)

Lower trace: Depression in adduction (*contracted*)

Base line 50 cycle interference

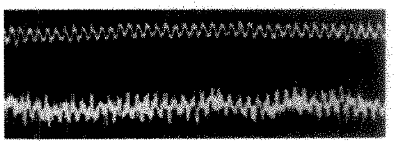

FIG. 6 *Case 2. E.M.G., left inferior oblique*

Upper trace: Depression in adduction (*relaxed*)

Lower trace: Attempted elevation in abduction (*contracted*)

Base line 50 cycle interference

Case 3, a 29-year-old man gave a 10-year history of intermittent horizontal and vertical diplopia and complained of increasing difficulty in maintaining binocular single vision. There was no history of facial or head trauma.

Examination

Visual acuity 6/5 in each eye.

OCULAR MOTILITY

Downdrift of each eye on adduction with poor elevation in adduction (See Hess chart, Fig. 7).

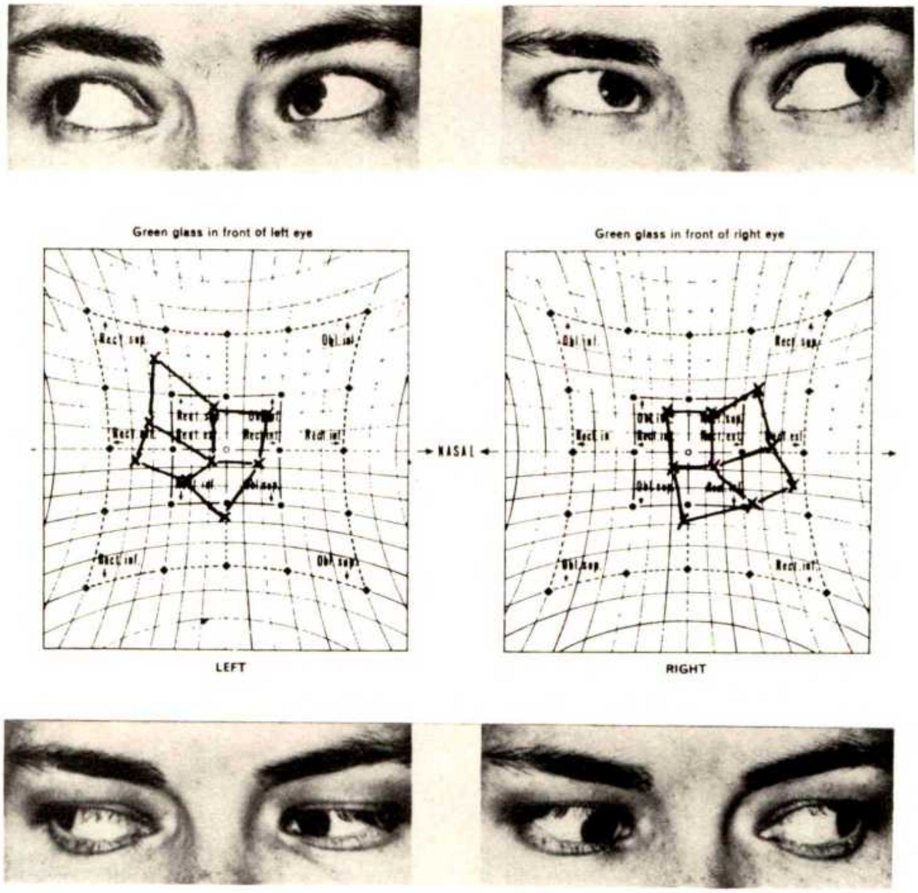

FIG. 7 *Case 3. Hess chart. Bilateral pseudoparesis of inferior obliques. Bilateral overaction of the superior rectus and superior oblique muscles. Depression of the adducting eye on left and right gaze*

PASSIVE DUCTION TEST

Elevation in adduction restricted in both eyes.

Diagnosis

Bilateral superior oblique tendon sheath syndrome.

EMG

Recordings were obtained from the left obliques only. Normal firing patterns were recorded on contraction and relaxation (Figs 8 and 9, opposite).

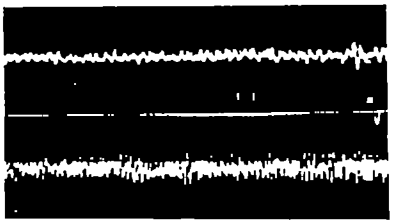

FIG. 8 *Case* 3. *E.M.G., left superior oblique*

Upper trace: Attempted elevation in adduction (*relaxed*)

Lower trace: Depression in adduction (*contracted*)

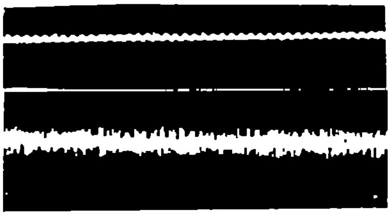

FIG. 9 *Case* 3. *E.M.G., left inferior oblique*

Upper trace: Depression in adduction (*relaxed*)

Lower trace: Attempted elevation in abduction (*contracted*)

Results

Recordings of electrical activity obtained from three adult patients with a clearly defined superior oblique tendon sheath syndrome showed the following features:

(1) On attempted elevation in adduction there was electrical silence from the superior obliques and maximum activity from the inferior obliques.

(2) On depression in adduction there was electrical silence from the inferior oblique and maximum activity from the superior oblique.

(3) The amplitude and frequency of the potentials obtained from the contracting superior oblique were constantly of a lower order of magnitude than those recorded from the contracting inferior oblique in spite of repeated sampling from different sites within the muscle bellies.

Discussion

The superior oblique tendon sheath syndrome has been classified as a musculo-fascial anomaly, along with the vertical retraction syndrome, strabismus fixus, and Duane's syndrome. These conditions were thought to occur as a result of disordered differentiation of paraxial mesoderm in intrauterine life (Catford, 1966).

Electromyographical studies on cases of Duane's syndrome have shown, however, anomalous patterns of electrical discharge from the horizontal recti in a large proportion of cases. Undiminished or increased activity has been recorded from the lateral rectus on adduction as well as co-contraction of the medial rectus on attempted abduction (Sato, 1960).

Defects of supranuclear innervation (Blodi, van Allen, and Yarbrough, 1964) and an abnormal peripheral nerve supply to the lateral rectus (Hoyt and Nachtigäller, 1965) have been suggested as possible causes. Abnormal recordings were observed from the vertical recti in cases with congenital paresis of the lateral recti (Papst and Esslen, 1964) and co-contraction of the oblique muscles in one case of the tendon sheath syndrome on elevation in adduction (Stein and Papst, 1958).

Our investigations of discharge patterns from the oblique muscles in the superior oblique tendon sheath syndrome revealed no evidence of co-contraction but only smooth recruitment of electrical activity from the relaxed to the maximally contracted state. These results show no deviation from Sherrington's law and agree with those of the first worker to investigate this syndrome electromyographically (Breinin, 1957).

The lower amplitude and frequency of potentials recorded from the contracting superior oblique as opposed to the activity recorded from the contracting inferior oblique suggests that fewer motor units were being activated in the former muscle. Since we have insufficient data on the electromyography of superior oblique muscles in patients with no ocular motility problems, further research is required to determine the significance of this finding.

Summary

A study of the electromyographical activity of the oblique muscles supports the view that the superior oblique tendon sheath syndrome is due to a local mechanical problem caused by the inability of the tendon to pass freely and to its full extent through the sheath.

We are indebted to Miss J. Behrman for her technical assistance and to the Audio-Visual Department of the Institute of Ophthalmology for producing the illustrations. We also thank the Surgeons of Moorfields Eye Hospital for referral of their patients to the Electro-Diagnostic Department and Miss J. Lace for secretarial services.

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Lowering of intraocular pressure in the untreated eye after the use of topical steroids

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The effect of steroids on intraocular pressure (IOP) has been interesting to ophthalmologists since reports of the effect of ACTH (Stern, 1953; François, 1954) and of topical steroids (Linnér 1959, a, b; Goldmann, 1962) were first published. It has been suggested that steroids act on the trabecular meshwork at the angle of the anterior chamber (Goldmann, 1962; Becker and Mills, 1963), probably by causing mucopolysaccharide deposition, and thereby reducing the pore size (Armaly, 1965; Lieb, 1963) and consequently the outflow facility of aqueous humour.

The hereditary nature of chronic simple glaucoma (Miller and Paterson, 1962; Armaly, 1967a) and of the steroid-induced rise in IOP (Armaly, 1966 a, b) are now well established. The sharing of similar genetic determinants by diabetes mellitus and chronic simple glaucoma has also been demonstrated (Armaly, 1967 b).

In this investigation the short-term and long-term effects on both eyes of the administration of topical steroids to one (the treated) eye have been studied. The effect of topical steroids on the treated eye is well documented (Armaly 1963 a, b; Becker and Mills, 1963; Levene, Wigdor, Edelstein. and Baum, 1967; Ramsell, Trillwood, and Draper, 1967), but that on the untreated eye has received little attention.

Methods and material

I. SHORT-TERM EFFECTS

Thirty patients were examined over a 2½ hr period. There were 26 cases of medically-controlled chronic simple glaucoma, three known steroid responders, and one case of simple ocular hypertension.

Both eyes of each patient were anaesthetized with Novesine (0·4 per cent.) and fluorescein mixture. The IOP was measured with a Goldmann applanation tonometer on a Haag-Streit 900 slit lamp.

Gutt. dexamethasone (0·05 per cent.) were instilled into one eye only of each patient. The eye to be treated was chosen by random selection throughout this study. The IOP was measured in both eyes 30 min. later. A further instillation of gutt. dexamethasone was then made into the same eye, and after another 30 min. the IOP was measured for a period of 2½ hrs.

II. LONG-TERM EFFECTS

55 patients were examined every week for 6 weeks. There were forty cases of medically-controlled chronic simple glaucoma and fifteen of simple ocular hypertension. None of these patients had had any previous intraocular surgery.

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The IOP was measured in both eyes of each patient using the same technique as in the first series. The nature of the project was explained so that the patients could be expected to follow their instructions correctly (Spaeth, 1970). They were asked to instil gutt. dexamethasone (0·5 per cent.) three times daily into one eye only. Patients who were having antiglaucoma therapy before this trial were instructed to continue with their regime as usual in addition to the dexamethasone drops. They were examined every week for 6 weeks at the same time of day to allow for diurnal variation (Lawton Smith, 1962).

To avoid observer bias the IOP was measured in both eyes before it was known which eye had been treated with dexamethasone.

Results

I. SHORT TERM

The initial IOP was compared with that recorded after 2½ hrs steroid instillation in both eyes for each patient. A paired data programme was used to analyse the results in the computer. Students' "t" test was done.

There was no significant change in IOP over the 2½ hrs period in either eye.

II. LONG TERM

The initial IOP for each eye was compared with that recorded each week for the same eye.

Out of 55 patients, twenty were found to have a rise of 6 mm.Hg or more in the treated eye during the 6 weeks of the trial. In these patients, designated "responders" (Armaly, 1965), the IOP rose significantly in both eyes (Table).

The other 35 patients were designated "non-responders". In this group the IOP showed little change in the first 4 weeks but did rise significantly in the 5th and 6th weeks in the treated eye. There was, however, a gradual and significant fall in the IOP in the untreated eye beginning from the 3rd week (Table).

Table *Results in responders and non-responders in Series II*

Group	*Responders*				*Non-responders*			
Eye	*Treated*		*Untreated*		*Treated*		*Untreated*	
IOP (mm. Hg)	*Change*	*P*	*Change*	*P*	*Change*	*P*	*Change*	*P*
Week 1	+ 6·1	<0·001	+2·5	<0·05	−0 5	Nil	−0·9	Nil
2	+ 8·2	<0·001	+3·2	<0·01	+0·3	Nil	−1·4	<0·01
3	+11·6	<0·001	+3·2	<0·01	+1·3	<0·02	−1·9	<0·001

Discussion

The most significant finding was that the application of topical steroids to one eye can cause a fall in the IOP in the other eye in the "non-responder" group. This important fact appears to have been overlooked by most authors. Armaly (1966) noted a fall in IOP (0·9 mm.Hg) in the untreated eye in normal patients, but found it to be statistically insignificant.

This investigation also confirms the rise in IOP in the "responders" previously reported in the treated (Armaly 1963, a, b; Becker and Mills 1963) and untreated (Armaly 1966 a, b) eyes, though this rise was less in the untreated eye.

To explain these significant but paradoxical results, we suggest that a humoral mechanism controls the IOP. A neural reflex for the control of IOP was considered but disregarded, because no significant change was observed in the short-term trial.

There is other evidence to support the idea of the humoral control of IOP:

(1) Lawton Smith, Stempfel, Campell, Hudnell, and Richman (1962) showed that diurnal variation in IOP was closely related to diurnal variation of plasma 17-hydroxycorticosteroid and that the height of the IOP corresponded to plasma steroid peaks.

(2) Raised IOP in cases of Cushing's syndrome reverted towards normal after the removal of cortisol-producing tumours (Neuner and Dardenne, 1968).

There is also evidence that topically-administered steroids are absorbed in sufficient amounts to produce systemic effects:

(*a*) A 2½-year-old child, who was having topical steroid therapy for uveitis, developed cushingism during treatment (Musson and Sloan, 1968).

(*b*) The topical use of dexamethasone has been shown to cause a reduction in urinary ketosteroids (Burch and Migeon, 1968).

(*c*) A patient with an allergy to citrus fruit showed an alleviation of the allergic symptoms when topical steroids were instilled into the eye (Nursall, 1965).

A systemic dose of dexamethasone causes a depression in plasma cortisol level. There is evidence that the plasma cortisol depression response differs in the responder and non-responder groups. Levene and Schwartz (1968) examined plasma cortisol levels before and 24 hrs after an oral dose of 0·75 mg. dexamethasone in a series of patients who had previously had steroid provocation tests. Patients with a high rise in ocular pressure rise (*i.e.* the responders) showed little depression in plasma cortisol, but those with the smallest ocular pressure response (*i.e.* the non-responders) showed a significant depression in plasma cortisol.

It is likely that the ability of dexamethasone to suppress the plasma cortisol level is genetically determined. Topically administered dexamethasone is absorbed into the general circulation in a concentration sufficient to suppress plasma cortisol levels. In the non-responders this suppression of plasma cortisol may cause a fall in the IOP in the untreated eye, while the direct action of dexamethasone on the treated eye prevents a parallel fall in IOP. In the responders, however, the plasma cortisol level is not suppressed and the direct effect of dexamethasone on the trabecular meshwork causes a rise in IOP in the eye receiving dexamethasone, while the small amount of absorbed dexamethasone combined with the unsuppressed plasma cortisol level also results in a slight rise in the IOP in the untreated eye.

This humoral nature of IOP control and the relationship between the plasma cortisol level and the IOP are now being studied.

Summary

The effect of short-term and long-term topical dexamethasone was observed in glaucomatous and ocular hypertensive eyes. In the "responder" group in the second series, there was a highly significant rise in the IOP in the treated eye and a smaller but significant rise in the untreated eye. In the "non-responder" group the IOP was lowered in the untreated eye. The mechanism of these different responses are discussed.

This work was carried out in the Glaucoma Clinic, Moorfields Eye Hospital, under the direction of Mr. Redmond J. H. Smith, to whom our thanks are due. We are also indebted to Mr. Redmond Smith and Mr. R. F. Fisher for their helpful criticism in the preparation of this paper.

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Emergence point and angulation of disc vessels in the normal eye

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The appearance of vessels in a pathological cup has been described as that of a shift nasally with a "break" of the vessels at the margin of the cup (Duke-Elder, 1959, Adler, 1962). Goldmann (1956) describes two typical forms of *normal* disc appearances, one in which there is a small amount of temporal excavation and the other in which excavation is more extensive, but in both forms the vessels arise at right angles to the cribriform plate at the nasal border of the cup; his first sign of glaucomatous change is the nasal displacement of the blood vessels, *i.e.* their angular deviation from their normal perpendicular ascent along the steep nasal slope of the physiological excavation. Although most observers would agree that this angular deviation is very common in glaucoma, Armaly (1969) has shown that in the normal eye "displacement" of the vessels, *i.e.* the angle between the major trunks and the floor of the cup at their point of entry, is related to the ratio of diameter of the optic cup to diameter of optic disc (the cup-to-disc diameter ratio).

A basis for the present survey was a clear distinction between two characteristics of the emerging disc vessels:

(*a*) *Emergence point, i.e.* the site at which vessels first became visible to the ophthalmoscopist, or rather to the fundus camera; the point is defined in relation to the margins of the disc and cup;

(*b*) *Angulation, i.e.* the angle between the emerging vessels and a plane tangential to the cribriform plate or base of the cup itself (see Fig. 1, overleaf).

Figs 4*a* and *b* are good examples of discs which differ in these characteristics. The term "bending" has not been used because it implies a change in direction, and we have no definite information about the pathway of the vessel behind the point where it becomes visible; "bending" might be better reserved for the change in direction of the vessel at the edge of the disc.

For a series of "normal" eyes, the following observations were made:

(1) With reference to the cup:
(*a*) The emergence position of the vessels in relation to:
 (i) the margins of the cup
 (ii) the area of disc cupping.
(*b*) The relationship between vessel angulation and emergence position.

(2) With reference to the disc:
(*a*) The emergence position of the vessels in relation to:
 (i) the margins of the disc
 (ii) the area of disc cupping.
(*b*) The relationship between vessel angulation and emergence position.

(3) The relationship between vessel angulation and the area of disc cupping.

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(4) The role of the eccentric position of the cup within the disc area in any relationships found under the above headings.

Subjects

The individuals used for this survey had been studied previously in the determination of the relationship between cup-to-disc ratio and length of eyeball (Tomlinson and Phillips, 1969) and applanation tension and length of eyeball (Tomlinson and Phillips, 1970). These were 75 undergraduates whose ages varied between 18 and 27 years; 26 were female and 49 male. The results from only one eye of each subject were used for statistical purposes; this was randomly selected by the toss of a coin (36 right, 39 left).

Method

Stereoscopic fundus photographs of all subjects were taken with the Zeiss Fundus Camera by the successive photographic technique described previously (Tomlinson and Phillips, 1969). These photographs were mounted on card to form stereo-pairs and viewed through a variable prism stereoscope.

The EMERGENCE POSITION of the vessels was referred to the horizontal and vertical margins of the cup and disc to give the *nasal/temporal emergence point ratio* (N/T EPR) (distances b/a for the cup in Fig. 2); and the *superior/inferior emergence point ratio* (S/I EPR) (distances c/d in Fig. 2). The point of emergence was taken to correspond to the mid-point of the vessel. Measurements were made on the stereo-pairs by a finely graduated steel rule. The cup-to-disc area ratio had been found in a previous survey by planimetry (Tomlinson and Phillips, 1969).

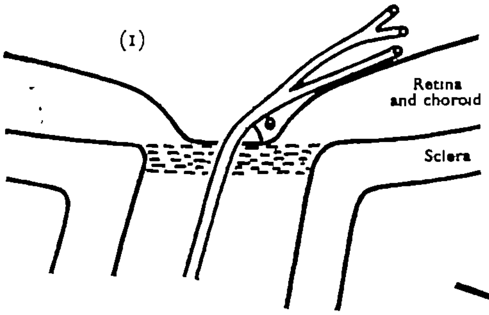

FIG. 1 *Vessel angulation. The angle ascribed to the vessel is that formed by the wall of the vessel immediately after emergence and the tangent to the lamina cribrosa at that point (angle = θ)*

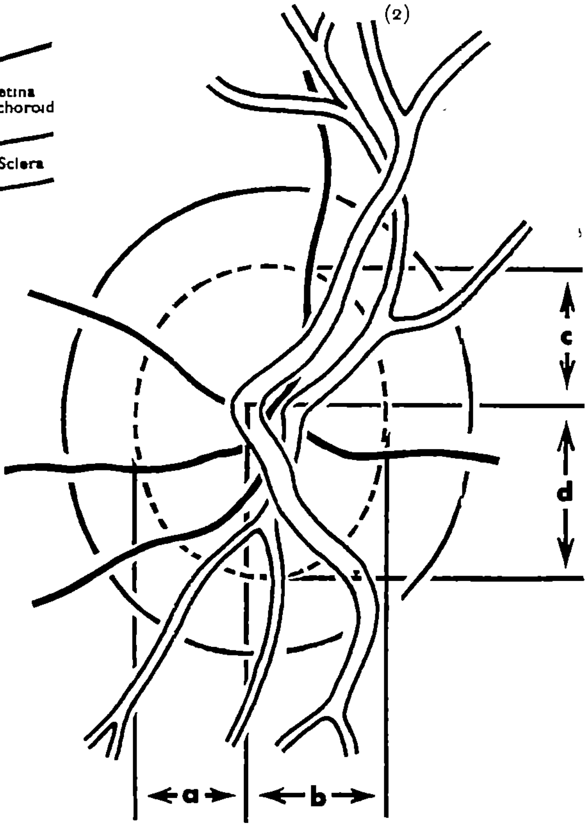

FIG. 2 *Diagram of right optic disc. Emergence Point Ratio (EPR) for the cup. — The nasal/temporal EPR is given by the ratio b/a,; the superior/inferior EPR by c/d*

The DEGREE OF ANGULATION of the vessels was found from the angle formed by the wall of the vessel immediately after emergence in the bottom of the cup and the tangential plane to the lamina cribrosa (plane assumed if lamina not visible) at the emergence point (Fig. 1). The angulation was measured in degrees of arc: if the vessels appeared to leave the base of the cup without bending and came straight towards the observer, the angle was recorded as 90°; if the vessels' direction on emergence was along the base of the cup, their angulation was 0°.

The emergence point ratios and the degrees of angulation were found separately for the arteries and veins.

The HORIZONTAL ECCENTRICITY of the position of the cup within the disc margins was expressed as the ratio of (*i*) the horizontal distance from the nasal edge of the cup to the nasal edge of the disc to (*ii*) the horizontal distance from the temporal edge of the cup to the temporal edge of the disc.

Results

(1a) EMERGENCE POINT RATIO (EPR) OF VESSELS IN THE CUP IN RELATION TO THE CUP-TO-DISC AREA RATIO

The relationship between the EPR (N/T and S/I) for the arteries and veins and the cup-to-disc area ratios were statistically analysed with the Rank Correlation method of Spearman (Table I). Significant relationships were found, for the vein, between the S/I EPR and the C/D area ratio and between N/T EPR and C/D area ratio; the larger the C/D area ratio the more inferior and nasal was the emergence position of the vein within the cup. A scattergram of the latter is shown in Fig. 3*a* (overleaf) together with a regression line of values of C/D area ratio on values of N/T EPR for the vein.

Table I *Rank correlation test applied to Emergence Point Ratio (EPR as related to the cup margins) compared with cup-to-disc area ratios and angulation of vessels and eccentricity of cup.*

Dimensions	*Correlation coefficient*	*Level of significance*
C/D area ratio and Artery N/T EPR	−0·090	P < 0·50*
C/D area ratio and Vein N/T EPR	−0·262	P < 0·50†
C/D area ratio and Artery S/I EPR	+0·090	P < 0·05*
C/D area ratio and Vein S/I EPR	+0·233	P < 0·05†
Artery angulation and Artery S/I EPR	+0·232	P < 0·05†
Artery angulation and Artery N/T EPR	−0·226	P < 0·05†
Vein angulation and Vein S/I EPR	+0·070	P < 0·05*
Vein angulation and Vein N/T EPR	−0·257	P < 0·05†
Horizontal cup eccentricity and Artery N/T EPR	−0·480	P < 0·001†
Horizontal cup eccentricity and Vein N/T EPR	−0·328	P < 0·01†

*Not significant
†Significant at the levels stated (< 0·05 is the minimum usually required level)

(1b) EMERGENCE POINT RATIO (EPR) OF VESSELS IN THE CUP IN RELATION TO VESSEL ANGULATION

In Table I are listed the significant relationships found between angulation and the EPR (S/I and N/T) for the artery, and between angulation and the N/T EPR for the vein. These indicate that the nearer the angulation of the artery is to 90° the more inferior and nasal is the emergence position of the vessel. The vein is similarly related in its emergence position in the horizontal meridian to vein angulation. A scattergram with a regression line of values of vein angulation on values of vein N/T EPR for the cup is shown in Fig. 3b.

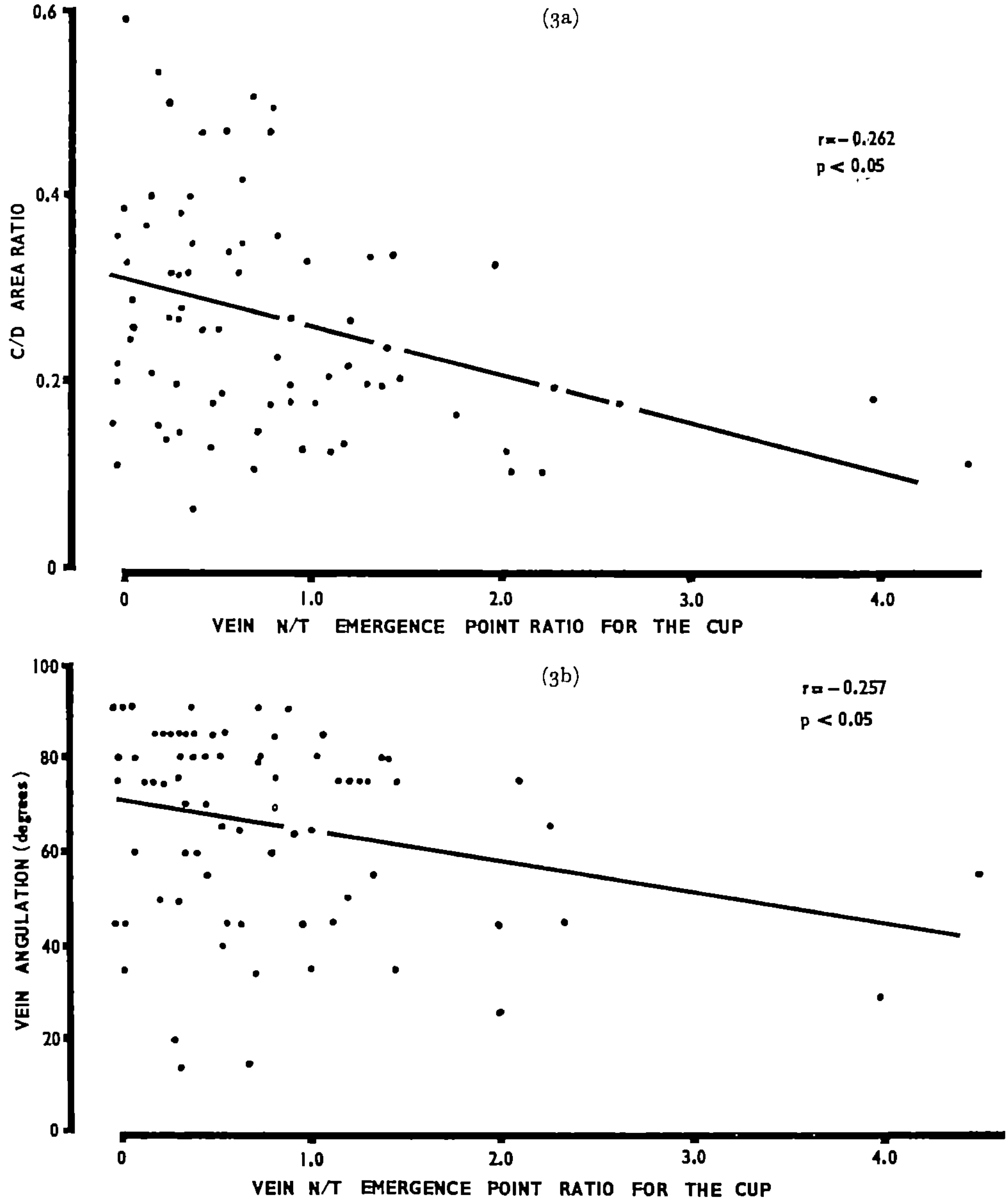

FIG. 3 *Scattergrams (with regression lines)*
(*a*) C/D area ratio on vein N/T emergence point ratios for the cup
(*b*) Vein angulation on vein N/T emergence point ratios for the cup

(2a) EMERGENCE POINT RATIO (EPR) OF VESSELS IN THE DISC IN RELATION TO CUP-TO-DISC AREA RATIO

In Table II are listed the significant relationships found between the N/T EPR of the vein and artery and the C/D area ratio; the larger the C/D area ratio the more nasally emergent are the vessels within the disc area. A scattergram with a regression line of values of C/D area ratio on values of vein N/T EPR for the disc is shown in Fig. 3c.

Table II *Rank correlation test applied to Emergence Point Ratio EPR (as related to the disc margins) compared with cup-to-disc area ratios and angulation of vessels and eccentricity of cup. Also eccentricity of cup compared with vessel angulation*

Dimensions	*Correlation coefficient*	*Level of significance*
C/D area ratio and Artery N/T EPR	−0·503	P < 0·001†
C/D area ratio and Vein N/T EPR	−0·339	P < 0·01†
Artery angulation and Artery N/T EPR	−0·097	P < 0·50*
Vein angulation and Vein N/T EPR	+0·090	P < 0·50*
Artery N/T EPR for Disc and cup	+0·486	P < 0·001†
Vein N/T EPR for Disc and cup	+0·758	P < 0·001†
C/D area ratio and Artery angulation	−0·340	P < 0·01†
C/D area ratio and Vein angulation	−0·430	P < 0·001†
Horizontal cup eccentricity and Artery N/T EPR	−0·094	P < 0·50*
Horizontal cup eccentricity and Vein N/T EPR	−0·043	P < 0·50*
Horizontal cup eccentricity and Artery angulation	+0·042	P < 0·50*
Horizontal cup eccentricity and Vein angulation	−0·089	P < 0·50*
Horizontal cup eccentricity and C/D area ratio	+0·265	P < 0·05†

*Not significant †Significant at the levels stated

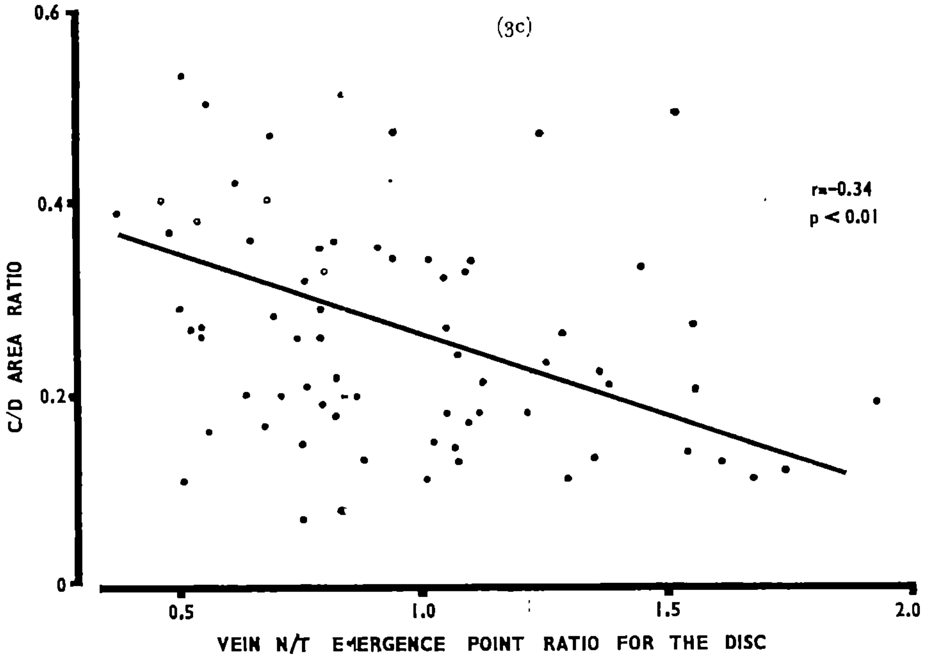

FIG. 3 (*c*) C/D area ratio on vein N/T emergence point ratios for the disc

(2b) EMERGENCE POINT RATIO (EPR) OF VESSELS IN THE DISC IN RELATION TO ANGULATION

No significant correlation was found for the N/T EPRs of the vein and artery and vessel angulation.

(3) VESSEL ANGULATION AND AREA OF DISC CUPPING

Highly significant relationships were found between vessel angulation and the C/D area ratio for both the vein and artery; the larger the C/D area ratio the more likely are the vessels to deviate from the 90° direction (Table II).

(4) CUP ECCENTRICITY

The cup was found to be significantly more eccentrically positioned with respect to the disc margins with larger cup-to-disc area ratios. A significant relationship was also found between cup eccentricity and the N/T EPR, with respect to the cup margins, for both veins and arteries; *i.e.* when the cup is eccentrically positioned within the disc area the more likely are the vessels to emerge to the nasal side (Table I). No correlation was found between the N/T EPR for vein or artery referred to the disc margin and cup eccentricity. A similar lack of correlation between vessel angulation and cup eccentricity can be seen in Table II.

Table III shows the mean and standard deviations for the emergence point ratios (in relation to the edges of the cup) and angulations recorded for the arteries and veins. Significant differences were found to exist on the Student's t test for the means of N/T EPR, S/I EPR and angulation between the veins and arteries. On the Snedecor F test a significant difference between the variances of vein and artery N/T EPR, and vein and artery angulation were found (See Discussion).

Table III *Means and standard deviations of vessel relationships to cup margins*

Dimension	*Mean* ± *S.D.*	*Level of significance of difference between means* (*t test*)	*Level of significance of difference between variances* (*F test*)
Vein N/T EPR Artery N/T EPR	0·83 ± 0·67 0·34 ± 0·34	$P < 0{\cdot}001$†	$P < 0{\cdot}01$†
Vein angulation Artery angulation (in degrees from "straight ahead")	65·4 ± 19·86 71·93 ± 13·46	$P < 0{\cdot}05$†	$P < 0{\cdot}05$†
Vein S/I EPR Artery S/I EPR	1·067 ± 0·35 1·144 ± 0·38	$P < 0{\cdot}05$†	$P < 0{\cdot}25$*

*Not significant †Significant at the levels stated

Discussion

The method of measurement of angulation used in this survey may be criticised on the basis of its subjective nature. One observer's impression was used throughout to describe the amount of angulation in degrees of arc. It is likely that this observer's idea of the angles in absolute terms was inexact, but the comparison between one subject and another was probably reasonably accurate. To test this claim, angulation of the vein and artery was assessed on two occasions; the correlation between the results obtained on these two occasions was significant at the 2 per cent. level. Angles were described in degrees of arc rather than by the grades used by Armaly (1969), in order to conform with the principle of using all available gradation of the data; in other words, a value allotted to a reading near one end of a wide group would not be taken as identical with one near the other end. Admittedly in our series in practice the observer described angles in steps of 5°, *e.g.* 40°, 45°. (Another consideration when data are allotted to groups is that a *descriptive* classification is more immediately understandable than a *numerical* grading: for example, in grading angles of anterior chamber the use of the terms narrow, medium and wide, with narrow-medium and medium-wide to make six groups would be less obscure than, say, "Grades I to VI").

Angulation of both arteries and veins within the cup have been shown in this survey to be related to the amount of disc cupping in "normal" eyes; the larger the area of cupping the greater is the departure of the vessel's path from the "straight-ahead" direction. This is in agreement with the results of Armaly (1969) and casts serious doubt on the value of vessel angulation as an indicator of pathological cupping, because it is found in large cups even when these are not associated with glaucoma.

It has also been demonstrated that the more nasally emergent the vessel is *within the cup* the *less* likely is it to deviate from the 90° direction - see Fig. 4; accordingly, the *absence* of nasal angulation of vessels cannot be accepted as a valid contraindication of pathological cupping. The increased "supporting" effect experienced by the vessels the closer they are to the margin of the cup is presumably the explanation. However, N/T EPR in relation to disc margin is not (significantly) correlated with vessel angulation – the explanation for this is probably that the position of the cup within the disc varies to some extent independently of the position of the vessels.

The point of emergence of the vein (as distinct from its angulation) when related both to the cup and disc margins has been found to be significantly related to the area of disc cupping in that discs with larger amounts of cupping have the point of emergence of the vein more to the nasal side (Fig. 4). Accordingly a nasal point of emergence of the vein should not be a diagnostic feature in pathological cupping, *especially in the absence of nasal angulation.* The vein S/I EPR within the cup is also related to the degree of disc cupping; the larger the area of cupping the more inferior is the emergence position. The emergence

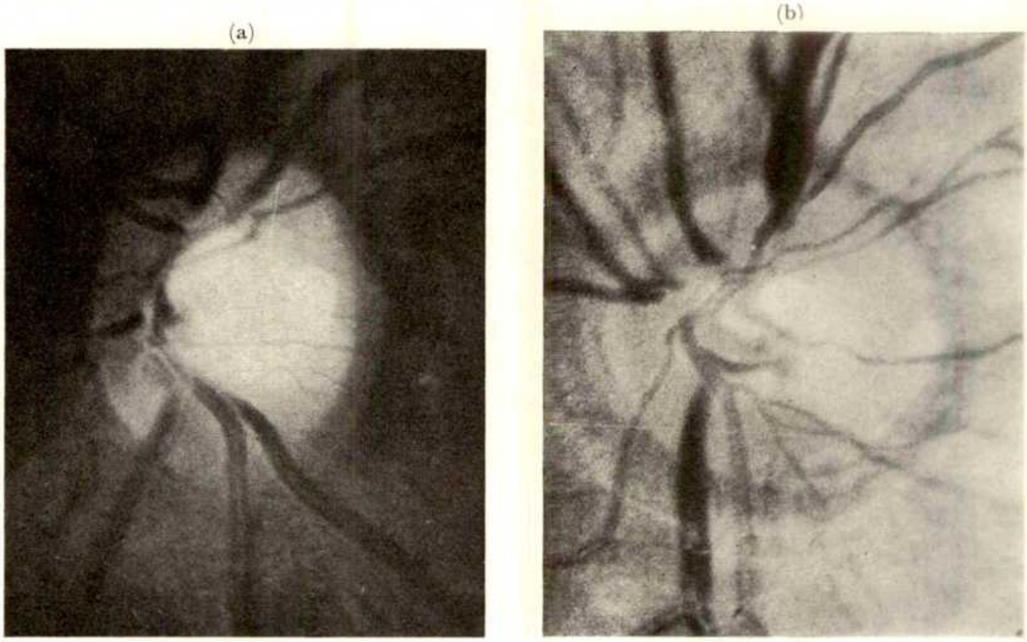

FIG. 4 *Photograph of optic disc in two subjects*

(*a*) The vessels emerge near the nasal edge of the cup *and* disc, at an angle of 85°; there is a moderate area of cupping (c/d area ratio = 0·40)

(*b*) The vessels emerge centrally within the cup *and* disc, and are more deviated from the "straight-ahead" direction (angle 15°); the degree of cupping is less (c/d area ratio = 0·32) ratios of the artery, both S/I and N/T, within the cup are not related to cup/disc ratio; this is consistent with the much smaller variation in artery emergence position in comparison with that of the vein (Table III).

As shown in Table III, the vein was found to emerge significantly more centrally within the cup than the artery, and its emergence position was susceptible to greater variation in emergence position in the horizontal meridian with increased cup/disc ratio. It also shows greater degrees of deviations from 90° than the artery. The vein relative to the artery may generally be described as emerging more temporally and a little superior within the cup and to be more angled in the initial part of its path. The relation between emergence points of vein and artery found in this survey agrees with that shown in diagrams in Wolff (1948) and Hayreh (1970).

An apparently low N/T EPR for a vessel in a cup, indicating nasal emergence of that vessel within the cup, may be due either to the vessel's emerging nasally within the disc area or to the cup's being eccentrically displaced towards the temporal margin. If the latter be true, it might be the reason for the significant correlation found between vein NT/ EPR for the cup and C/D area ratio (cup eccentricity has been shown to be related to cup-to-disc area ratio (Table II) and to vein N/T EPR for the cup). The eccentricity of the cup cannot, however, have any effect on the vein N/T EPR for the *disc*. As a high correlation has been demonstrated at the 0·01 per cent. level of significance between N/T EPRs for the cup *and* disc for both the arteries and vein, we consider that the relationship found between cup-to-disc area ratio and vein N/T EPR for the cup is almost independent of cup eccentricity and instead due almost entirely to the emergence point of the vein. Cup eccentricity is not found to be related to vessel angulation or to the emergence point ratios for the disc, and its importance in the observations listed above can be considered to be small.

Some clinical implications

These observations tend to confirm that the criteria for diagnosis of *early* pathological cupping are difficult to define in an individual case. Emergence point ratios of vessels should probably play no part in the diagnosis, save in the negative sense that *if the emergence point is markedly eccentric, angulation of the vessels should not be expected even if the disc is pathologically cupped.* Angulation of vessels (as well as cup-to-disc ratios) in individual cases at one point in time cannot claim to do more than support suspicion; in other words, it is illogical to conclude that, because angulation of the vessels at the bottom of the established pathological cup is very common, glaucoma is to be diagnosed when angulation is present.

Authors vary in the value they place on the presence of pathological cupping in the diagnosis of open-angle glaucoma. Graham and Hollows (1966) showed that ophthalmoscopy was as efficient in detecting *established* (our italics) glaucoma as tonometry and field screening, although a high false positive rate was noted (no false negatives). Fisher, Carpenter, and Wheeler (1970) found a close relationship between the state of the disc and the size of the field - this correlation was greater, with one exception, than the correlations between any other two variables which included ocular tension and facility of outflow; however, a category of "doubtful" cupping was included. Armaly (1969) would seem to agree with Shutt, Boyd, and Salter (1967) that a fair proportion of cases with glaucomatous field loss exist *without* pathological cupping (34 per cent. according to the latter). In so far as there may be a true difference of opinion between authors (it may be less than appears because some are concerned with early cupping and others with established glaucoma), differing criteria are probably the explanation. It would probably be common ground, however, that the diagnosis of *early* pathological cupping is often difficult and that tonometry, visual field examination, and careful examination and recording of the appearances of the optic disc, as well as slit-lamp examination and gonioscopy would constitute the minimum criteria for the diagnosis and management of glaucoma.

It seems likely that ophthalmoscopic criteria for early pathological cupping would be best derived in the individual case from serial stereoscopic photographs of the disc – or diagrams made regularly.

We have the clinical impression that sharpness of the disc margin is a good criterion of early as well as of late pathological cupping. Vessels are of little help in this assessment because the points at which they cross the disc margin are affected rather late in the pathological process. Sharpness has to be discounted, however, as of no pathological significance along a temporal crescent or a (minimal) inferior coloboma. Another important characteristic is saucerization of the disc tissue between the physiological cup and the disc margin. Pallor and excavation with undermining of the disc margins are late signs.

Summary

The angulation and site of emergence of the vessels relative to the margins of the cup and disc are considered in relation to the area of disc cupping (the cup-to-disc or C/D area ratio) in a series of 75 normal eyes of subjects whose ages ranged from 18 to 27 years. Significant relationships are found to exist between the "emergence point ratios" for the vein (*i.e.* distance between centre of emerging vein and nasal edge of cup or disc divided by distance from temporal edge) and C/D area ratio; and between the emergence point ratio of the artery when referred to the disc margin only (not cup) and the C/D area ratio. Discs with larger C/D area ratios have vessels which emerge more to the nasal side. Eyes with larger C/D area ratios tend to have vessels which are more angled on emerging into ophthalmoscopic view. A relationship between vessel angulation and emergence position, referred to the cup margin, is also found to exist (*i.e.* vessels which emerge towards the nasal edge do so at angles near to 90° to the base of the cup). The influence of the eccentricity of the cup within the disc margins on the above relationships is probably small. The validity of vessel angulation and nasal emergence point of vessels as diagnostic features in glaucoma and the *absence* of nasal angulation as a contraindication of pathological cupping are brought into question by the results of this survey.

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Causes of enucleation as seen in Jerusalem

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Following the report on causes of enucleation in Uganda (Davanger, 1970), it was felt desirable to make a similar study of cases seen at our hospital in Jerusalem. This comparison is likely to prove interesting because therapeutic developments may be expected to alter the pattern of cause and effect in the coming years.

Material

The data were collected from the hospital records for the years 1965 to 1969. During the first half of the period the hospital with its eighty beds was situated in Jordan and drew patients from all over the Middle East and beyond, but since June, 1967, it has been in the territory annexed by Israel. Some patients continued to come from Arab countries by Red Cross permit or under family reunion schemes, but most of them are now drawn from the million or so Arabs resident within Israeli-administered territory.

During the 5-year period, 409 eyes were removed by enucleation (the majority), evisceration, and exenteration of the orbit (2 cases only). Data were available for more detailed analysis for only 235 of the total. As in Uganda, almost all were treated as inpatients and the indications for enucleation were similar to those accepted in Europe.

Findings

The number of enucleations was calculated as a percentage of all outpatients, and also of all inpatients and of all operations on inpatients at the St. John Ophthalmic Hospital, These are compared in Table I, as in Davanger's article. The St. John's figures fall between those of Uganda and Berlin and the later figures from Basel.

Table I *Cases of enucleation as percentage of patients and operations compared with figures from Uganda, Basel, and Berlin*

Hospital	*St. John Hospital, 1965–69*		*Uganda*	*Basel*		*Berlin*
Cases	*Total new cases*	*Per cent. eyes enucleated*	1963–67	1935–39	1950–54	1925–35
Outpatients	142,490	0·29	0·2	0·5	0·2	0·5
Inpatients	12,126	3·4	5·4	4·7	2·0	—
Eye operations on inpatients	9,678	4·2	8·4	7·2	3·4	5·6

CAUSES OF ENUCLEATION (Table II, opposite)

An effort was made to discover the primary cause, *i.e.* the condition leading to removal of the eye, the immediate cause being of less interest. The frequent lack of a reliable history and the frequent appearance of a generally "disorganized eye" account for the large

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Table II *Causes of enucleation by diagnosis and sex in order of frequency*

Diagnosis	*Total cases*		*Sex*				*Male : female ratio*
			Male		*Female*		
	No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	
(1) Painful blind eye	60	25	37	27	23	24	1·6 : 1
(2) Corneal disease	59	25	31	23	28	29	1·1 : 1
(3) Trauma	43	18	31	23	12	12	2·6 : 1
(4) Phthisis bulbi	33	14	13	9	20	21	0·65 : 1
(5) Panophthalmitis	15	6	12	9	3	3	4·0 : 1
(6) Glaucoma	13	5	8	6	5	5	1·6 : 1
(7) Malignant tumour	12	5	6	4	6	6	1·0 : 1*
Total	235		138		97		

*0 to 9 year Age group 5 : 1

number in the "painful blind eye" group. The Middle East appears to be a peaceable place compared with Uganda, as known trauma appears in only 18 per cent. of cases compared with Uganda's 30 per cent.

(1) *Painful blind eye*

Had the primary cause been known, it is reasonable to suppose that these cases would have been fairly evenly divided between the more specific categories.

(2) *Corneal disease*

Complications following corneal ulceration and infection formed the largest specific group. This is confirmed by the large number of damaged corneae which require grafting. The current average of two corneal grafts a week is only half of what is required, the limiting factor being the lack of donor material. Malnutrition was considered to be a significant factor affecting healing in only a very few cases.

Trachoma, in the late stages of entropion and trichiasis, is still common in the area, but acute trachoma is now much less frequent.

(3) *Trauma*

Males are more than 2½ times as likely to lose an eye from trauma as females. In the age group 10–29 years known trauma was the cause of enucleation in nearly one-third of cases.

(4) *Phthisis bulbi*

The high percentage of the 10 to 29 year age group in which the cause was given as a "shrunken "eye reflects the preference at this "marriageable age" for a patient to have a prosthesis fitted for cosmetic reasons.

(5) *Panophthalmitis*

It was not easy to assess the primary cause in many of these patients, as they usually presented for the first time with the fully-developed condition. In some the disease may have been secondary to another infection but many could perhaps have been included under corneal disease. No explanation for the 4:1 male : female ratio is offered.

(6) *Glaucoma*

Many cases of glaucoma are not seen until the disease is far advanced. Primary cases only are included here, secondary cases being listed under their primary cause.

(7) *Malignant tumour*

All these cases were verified histologically. In the 0 to 9 year age group the male:female ratio was 5:1, but females predominated in the last three decades bringing the overall ratio to 1:1. There was one malignant lymphoma and one malignant melanoma amongst the 12 cases.

AGE AND SEX DISTRIBUTION (Table III)

There is a predominance of males in all age groups. Excluding the first decade the number of enucleations does not differ greatly between age groups but fewer enucleations were performed between the ages of 30 and 49 years.

Table III *Age and sex distribution of causes of enucleation (male + female).*

	Age group (yrs)															
Diagnosis	0–9		10–19		20–29		30–39		40–49		50–59		60–69		70+	
	No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	*No*	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*
Painful blind eye	1 (1 + 0)	5	3 (2 + 1)	9	5 (2 + 3)	16	8 (4 + 4)	33	8 (6 + 2)	27	13 (9 + 4)	38	9 (5 + 4)	30	13 (7 + 6)	42
Corneal disease	6 (4 + 2)	32	9 (2 + 7)	27	8 (7 + 1)	25	7 (4 + 3)	29	6 (2 + 4)	21	8 (5 + 3)	23	10 (4 + 6)	30	5 (3 + 2)	16
Trauma	4 (3 + 1)	21	10 (8 + 2)	30	9 (6 + 3)	28	4 (4 + 0)	17	6 (4 + 2)	21	2 (0 + 2)	6	3 (3 + 0)	9	5 (3 + 2)	16
Phthisis bulbi	—		9 (3 + 6)	27	9 (2 + 7)	28	4 (2 + 2)	17	5 (3 + 2)	17	2 (0 + 2)	6	3 (2 + 1)	9	1 (1 + 0)	3
Panophthalmitis	—		—		1 (1 + 0)	3	1 (0 + 1)	4	3 (3 + 0)	10	3 (2 + 1)	8	3 (3 + 0)	9	4 (2 + 2)	13
Glaucoma	2 (1 + 1)	10	1 (1 + 0)	3	—		—		1 (0 + 1)	3	4 (2 + 2)	12	3 (2 + 1)	9	2 (2 + 0)	6
Malignant tumour	6 (5 + 1)	32	1 (1 + 0)	3	—		—		—		2 (0 + 2)	6	2 (0 + 2)	6	1 (0 + 1)	3
Total	19 (14 + 5)		33 (17 + 16)		32 (18 + 14)		24 (14 + 10)		29 (18 + 11)		34 (18 + 16)		33 (19 + 14)		31 (18 + 13)	
Male : female ratio	2 8 : 1		1 : 1		1 3 : 1		1·4 : 1		1 6 · 1		1·1 : 1		1·3 : 1		1·4 : 1	

Summary

The primary causes of enucleations at the St. John Ophthalmic Hospital, Jerusalem, are reviewed and compared with those in a similar report from Uganda. Corneal disease is the most important cause (25 per cent.) and next in importance is trauma (18 per cent.).

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Intraocular pressure rebound

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Hyperosmolar solutions and digital massage are frequent adjuncts employed to minimize vitreous loss at cataract extraction (Scott, 1962; Virno, Cantore, Bietti, and Bucci, 1963; Murray and Tipler, 1966; Guyton, 1954; Kirsch and Steinman, 1955). The former is effective in reducing vitreous mass during the time interval usually necessary to complete a lens extraction, but the latter may not have great value in this regard. In rabbit experiments in the closed eye, within 5 minutes of the completion of massage, vitreous weight has reached its baseline (Obstbaum, Robbins, Best, and Galin, 1971). In patients, intraocular pressure has usually reached its lowest level within 15 minutes of the completion of 5 minutes of digital massage. In the open eye also, previous massage does not increase the vitreal water loss that occurs after simply opening the rabbit eye (Galin, Robbins, and Obstbaum, 1971).

Since the application of digital massage and the administration of hyperosmolar therapy are often carried out together, a study was initiated to determine if hyperosmolar vitreous dehydration could offset the phenomenon of compression vitreous rebound in rabbits.

Materials and methods

New Zealand albino rabbits of approximately 3 kg. were the experimental animals. Anaesthesia was effected with intravenous sodium pentobarbitol, 30 mg./kg. Vitreous weights were determined by a freezing technique which has been described elsewhere (Robbins and Galin, 1969). Essentially the method consists of enucleating the globes, freezing them with dry ice, dissecting the outer coats, and isolating the frozen vitreous spheroid. The vitreous masses are then weighed to within milligram accuracy.

Ten control animals were anaesthetized and both globes were enucleated and treated as above. In various groups of experimental animals digital massage was applied to one eye for 30 seconds and released for 2 seconds, the total massage periods varying from 1 to 10 minutes. Intraocular pressures were measured with a Schiotz tonometer calibrated for the rabbit eye at the end of each massage period and the eyes were then enucleated and appropriately handled (Robbins and Galin, 1969).

An aqueous solution of 20 per cent. mannitol, 2 g./kg., was rapidly infused into an ear vein after one eye of a group of rabbits was enucleated. The second eye was enucleated 60 minutes after the infusion terminated, and both eyes were frozen and ultimately dissected. Additionally, a group of rabbits underwent bilateral enucleation and processing 60 minutes after a mannitol infusion. Baseline and post-treatment intraocular pressures were also obtained. An additional group of animals underwent mannitol infusion as above, followed by 5½ minutes of digital massage before enucleation. The control eyes were enucleated either before the infusion or 60 minutes after the termination of the infusion, just before uniocular digital massage.

In another group of rabbits, compression of the eye for 5½ minutes was accomplished with 50 g. applied to the cornea with a Bailliart ophthalmodynamometer. The experimental eyes were enucleated at progressive time intervals after the termination of compression. Similar experiments were conducted in which ophthalmodynamometric compression was initiated 60 minutes after the termination of a mannitol infusion.

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Results

Table I lists the control vitreous weights in ten rabbits. The vitreous masses differ in weight by an average of only 0·22 per cent., indicating that one eye may readily be used as a control for the treated fellow eye.

Table I *Vitreous weights in control animals measured by a freezing technique*

Rabbit No.	*Vitreous weight (g.)*		*Per cent. difference*
	Left	*Right*	
1	2·040	2·032	0·39
2	1·778	1·780	0·11
3	1·850	1·846	0·22
4	1·586	1·582	0·25
5	1·340	1·345	0·37
6	1·893	1·896	0·16
7	1·374	1·379	0·36
8	2·009	2·007	0·10
9	1·540	1·540	0·00
10	2·072	2·068	0·19

Average weight variation = 0 22 per cent.
SD = 0·12 per cent.

Fig. 1 records the intraocular pressure change and the vitreous weight change resulting from ocular digital massage. It should be noted that the vitreous initially gains weight and then progressively decreases in weight with continued massage. All measurements were taken immediately after the massage so that no vitreous "rebound" was noted.

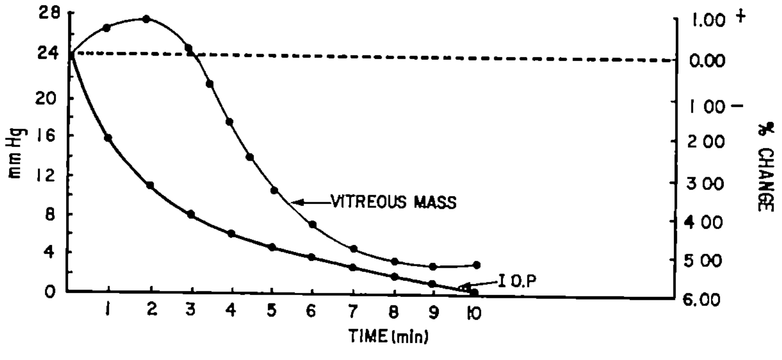

FIG. 1 *Influence of various periods of digital massage on intraocular pressure and vitreous weight*

Table II lists the effects of mannitol therapy in reducing intraocular pressure and, concomitantly, vitreous mass. In all cases, comparison between the treated eye and the untreated fellow eye shows mannitol inducing a distinct reduction of vitreous mass accompanying the fall in pressure.

Table III lists the intraocular pressures and vitreous weights 60 minutes after the completion of a 20 per cent. mannitol infusion. It is clear that hyperosmolar therapy reduces vitreous weight and does so in essentially equal degree to both eyes. Table IV records the effect of 5½ minutes of digital massage initiated 60 minutes after a 20 per cent. mannitol infusion on intraocular pressure and vitreous weight. It should be noted that in the unopened eye the vitreous weight reduction induced by hyperosmolar therapy is augmented by digital massage if measured immediately after massage.

Table II *Vitreous weight and intraocular pressure reduction induced by hyperosmolar mannitol*

Rabbit No.	*Vitreous weight (g.)*		*IOP decline with mannitol (Schiotz units 5·5 wt)*	*Per cent. weight loss with mannitol*
	Untreated eye	*After mannitol*		
11	1·638	1·572	3·0→12·5	4·03
12	1·720	1·653	3·0→11·5	3·90
13	1·683	1·620	3·5→12·0	3·74
14	1·506	1·452	3·0→12·0	3·58
15	1·908	1·834	4·0→14·0	3·88

Average weight loss = 3·83 per cent. SD = 0·15 per cent.

Table III *Comparison of vitreous weight and intraocular pressure change induced by hyperosmolar mannitol in both eyes of the same animal*

Rabbit No.	*Right*		*Left*		*Per cent. weight change Right v. Left*
	Vitreous weight after mannitol (g.)	*IOP change with mannitol (Schiotz units 5·5 wt)*	*Vitreous weight after mannitol (g.)*	*IOP change with mannitol (Schiotz units 5·5 wt)*	
16	1·600	3·0→11·0	1·598	3·0→10·5	0·13
17	1·540	3·5→10·0	1·530	3·5→10·0	0·65
18	1·810	4·0→11·5	1·812	4·0→11·0	0·11
19	1·747	3·0→10·0	1·743	3·0→10·0	0·23
20	1·928	3·5→12·5	1·934	3·0→13·0	0·31

Average weight variation = 0·29 per cent. SD = 0·14 per cent.

Table IV *Influence of digital massage on vitreous changes induced by hyperosmolar mannitol*

Rabbit No.	*Mannitol alone*			*Mannitol and massage*				*Per cent. weight loss from massage*
	Vitreous weight(g.)	*IOP changes (Schiotz units, 5·5 wt)*		*Vitreous weight(g.)*	*IOP changes (Schiotz units, 5·5 wt)*			
	After mannitol	*Before mannitol*	*After mannitol*	*After mannitol and massage*	*Before mannitol*	*After mannitol*	*After mannitol and massage*	
21	1·839	4·0	10·0	1·777	4·0	10·0	14·0	3·36
22	1·954	3·5	9·5	1·912	3·5	10·0	16·0	2·15
23	1·640	4·0	11·0	1·593	4·0	10·5	17·0	2·86
24	1·556	3·0	10·0	1·519	3·5	9·5	15·5	2·38
25	1·677	3·0	10·5	1·636	3·0	10·0	17·0	2·44
26	2·065	3·5	9·0	1·998	3·5	9·0	16·0	3·24
27	1·470	3·5	11·0	1·410	3·5	10·5	18·0	4·08
28	1·870	4·5	9·5	1·830	4·5	10·0	16·0	2·14
29	1·592	3·5	8·5	1·551	3·0	8·5	14·5	2 58
30	1·610	4·0	9·0	1·582	4·0	9·0	15·0	1·74

Average weight loss attributable to massage = 2·70 per cent. SD = 0·63 per cent.

Tables V to VIII list the effects of 5½ minutes of 50 g. of ophthalmodynamometric compression on intraocular pressure and vitreous weight at the end of compression and for varying periods thereafter. It should be noted that vitreous weight and intraocular pressure rebound become manifest approximately 5 minutes after compression ceases. Fig. 2 indicates that hyperosmolar therapy does not reduce compression rebound in the closed eye.

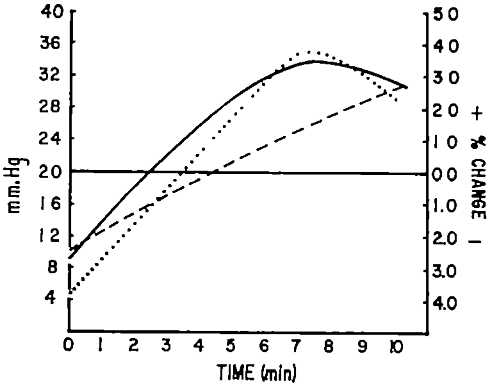

FIG. 2 *Influence of* 50/g. *ophthalmodynamometric compression on intraocular pressure and vitreous weight in the undisturbed eye and* 60 *min. after hyperosmolar mannitol*

Vitreous mass change

.... after mannitol and compression

------ after compression alone

IOP recovery

——— after compression

Table V *Effect of* 50 *g. ophthalmodynamometric compression on vitreous weight and intraocular pressure after* 5·5 *min. of compression*

	Control eye	*Experimental eye*			
		Before compression	*After* 5·5 *min. of* 50 *g. compressive force*		
Rabbit No.	*Vitreous weight* (*g.*)	*IOP* (*Schiotz units,* 5·5 *wt*)	*IOP* (*Schiotz units,* 5·5 *wt*)	*Vitreous weight* (*g.*)	*Per cent. weight change*
31	1·349	2·0	8·5	1·332	−1·26
32	1·361	3·0	9·0	1·325	−2·64
33	1·656	3·5	9·0	1·618	−2·29
34	1·393	2·5	8·0	1·347	−3·30
35	1·778	3·5	8·0	1·730	−2·69

Average vitreous weight change = 2·44 per cent. SD = 0·74 per cent.

Table VI *Effect of* 50 *g. ophthalmodynamometric compression on vitreous weight and intraocular pressure* 5 *min. after termination of* 5·5 *min. of compression*

	Control eye	*Experimental eye*				
		Before compression	*After* 5·5 *min. of* 50 *g. compressive force*	5 *min. after termination of compressive force*		
Rabbit No.	*Vitreous weight* (*g.*)	*IOP* (*Schiotz units,* 5·5 *wt*)	*IOP* (*Schiötz units,* 5·5 *wt*)	*IOP* (*Schiotz units,* 5·5 *wt*)	*Vitreous weight* (*g.*)	*Per cent. weight change*
36	1·442	3·5	8·5	1·5	1·434	−0·55
37	1·520	4·0	7·0	2·5	1·506	−0·92
38	1·518	2·5	8·0	2·0	1·510	−0·53
39	1·574	3·5	8·0	1·5	1·562	−0·76
40	1·536	5·5	10·0	3·0	1·525	−0·71

Average weight change = − 0·69 per cent. SD = 0·16 per cent.

Table VII *Effect of* 50 *g. ophthalmodynamometric compression on vitreous weight and intraocular pressure* 7 *min. after termination of* 5·5 *min. of compression*

	Control eye	*Experimental eye*				
Rabbit No.	*Vitreous weight (g.)*	*Before compression*	*After* 5·5 *min of* 50 *g. compressive force*	7 *min. after termination of of compressive force*		*Per cent. weight change*
		IOP (Schiötz units, 5·5 *wt)*	*IOP (Schiötz units,* 5·5 *wt)*	*IOP (Schiötz units,* 5·5 *wt)*	*Vitreous weight (g.)*	
41	1·458	4·0	9·0	1·0	1·481	+1·58
42	1·633	4·0	9·0	1·0	1·648	+0·92
43	1·552	3·0	8·0	1·0	1·572	+1·28
44	1·464	2·0	8·0	1·5	1·482	+1·22
45	1·618	3·5	8·5	1·5	1·639	+1·30

Average vitreous weight change = + 1·26 per cent. SD = 0·23 per cent.

Table VIII *Effect of* 50 *g. ophthalmodynamometric compression on vitreous weight and intraocular pressure* 10 *min. after termination of* 5·5 *min. of compression*

	Control eye	*Experimental eye*				
Rabbit No.	*Vitreous weight (g.)*	*Before compression*	*After* 5·5 *min. of* 50 *g. compressive force*	10 *min after termination of compressive force*		*Per cent. weight change*
		IOP (Schiotz units, 5·5 *wt)*	*IOP (Schiötz units,* 5·5 *wt)*	*IOP (Schiötz units,* 5·5 *wt)*	*Vitreous weight (g.)*	
46	1·384	4·0	9·5	2·0	1·416	+2·31
47	1·422	3·5	8·5	1·5	1·462	+2·81
48	1·493	2·5	8·5	1·0	1·523	+2·07
49	1·426	3·5	8·5	1·5	1·470	+3·09
50	1·430	2·5	8·0	2·0	1·470	+2·79

Average vitreous weight change = + 2·61 per cent. SD = 0·41 per cent.

Discussion

A series of studies from this laboratory has attempted to clarify the status of pre-incision manoeuvres used in lens extraction (Obstbaum and others, 1971; Galin and others, 1971; Robbins and Galin (1969); Robbins, Blumenthal, and Galin, 1970a; Robbins, Obstbaum, Best, and Galin, 1970b). Certain steps appear to be of benefit. Excellent akinesia is essential to prevent global and scleral retraction which might "shrink" the vitreous container. Retrobulbar anaesthesia, however, has no direct effect on vitreous weight (Robbins and others, 1970b). The use of hyperosmolar solutions also appears worthwhile since vitreous mass in the closed and open eye is reduced. Furthermore, this form of therapy appears to maintain effectiveness during the time usually needed to perform a lens extraction. Other drugs and manipulative measures appear to have little direct or indirect effect on the vitreous.

Digital massage may hasten motor and sensory akinesia and reverse their usual sequence, so that it augments the effects of retrobulbar anaesthesia (Gasser and Erlanger, 1929). It also reduces vitreous weight during the period of compression and for a short period thereafter. This manoeuvre in the rabbit, however, leads to an increase in intraocular pressure in the closed eye which starts approximately 5 minutes after massage is ended. Intraocular pressure and vitreous mass rebound is not reduced, and not eliminated, if massage is preceded by hyperosmolar therapy in the closed rabbit eye. Intraocular pressure rebound is uncommon in patients, but the weight and volume of the vitreous are unknown during the recovery phase of intraocular pressure, and need neither parallel nor reflect the state of the intraocular pressure.

If the eye is opened after digital massage has been completed and the vitreous is weighed sequentially, no increase in the normal vitreous weight loss that occurs on opening the eye is apparent. Furthermore, the beneficial effects of previous hyperosmolar therapy is not augmented by previous digital massage in the open eye model.

The most significant reductions in vitreous weight occur after simply opening the eye. Water progressively leaks from the vitreous so that its mass is progressively reduced. There is continued vitreal water loss without classic vitreous loss. Whether choroidal or subchoroidal volume changes immediately negate this effect is not known. This water loss can be augmented by hyperosmolar therapy, but is not changed by previous digital massage or by drugs such as acetazolamide. This latter agent also has no direct or indirect beneficial effect on vitreous weight (Robbins and others, 1970b).

It is always pleasant to watch air suck in as a lens is delivered indicating the creation of negative intraocular pressure. This phenomenon infers that nothing internal or external is decreasing the volume of the scleral shell. One is never certain, however, when this event will occur. When the eye is initially opened, bulging of the iris, furrowing of the cornea, and a host of other clinical hints alert the surgeon to rule out the presence of external pressure and he can act accordingly. Even these signs, however, may not be immediately apparent, as in a delayed retrobulbar haemorrhage. Unfortunately, save for the catastrophe of expulsive choroidal haemorrhage, no available laboratory or clinical data indicate whether the uvea or subchoroidal space is primarily involved in vitreous prolapse. Studies to evaluate these potentials as major causes of vitreous loss during operations for lens extraction are now being undertaken.

It appears from these studies that only a few of the present preoperative steps designed to minimize vitreous loss are truly effective, and that attempts to shrink the vitreous mass, though worthwhile, are probably not the best. The most useful measures appear to be the elimination of vitreous compression from within the globe or from outside.

Summary

Hyperosmolar mannitol reduces vitreous weight in the closed rabbit eye during the time usually required for a lens extraction, but digital massage has no such effect. The latter induces a vitreous rebound associated with an increase in intraocular pressure in the closed rabbit eye. Though mannitol reduces this rebound effect, it does not eliminate it.

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Visual fields in diabetic retinopathy

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Little attention has been given until recently to the visual field defects occurring in diabetic retinopathy.

Scott (1957) considered diabetes mellitus to be an extremely rare cause of scotomata. Livingston (1943) found similar scotomata within the central field which were unassociated with visible retinopathy and were thought to be caused by areas of local anoxia. Dubois-Poulsen (1952) described altitudinal field defects corresponding to major retinal arterial obliterations. Harrington (1964) considered the field defects occurring in diabetic patients to be non-specific.

Recently Roth (1969) has reported scotomata occurring within 20° of fixation in the presence of very mild diabetic retinopathy or without visible fundus lesions. Cotton-wool spots have been shown to cause scotomata (Williams, Drance, Harris, and Fairclough, 1970). Caird, Pirie, and Ramsell (1969) have pointed out the possibility that small visual field defects unassociated with visible retinopathy may precede observable fundus changes. It has been taken for granted and is common clinical experience that proliferative retinopathy and large haemorrhages cause significant field loss.

The purpose of this work was to study the visual field defects of patients with different grades of diabetic retinopathy and to correlate these defects with anatomical lesions in the fundus as seen by ophthalmoscopy, on fundus photographs, or on fluorescein angiography.

Material and methods

24 diabetic patients showing various levels of diabetic retinopathy were selected on the basis of their willingness to participate in the study and their ability to cooperate in the tests required.

Three patients who showed no ophthalmoscopic evidence of diabetic retinopathy all currently require insulin therapy and have had blood sugars above 250 mg./100 ml. serum. The visual acuity was 20/15 or 20/20 in all eyes.

Thirteen patients showed non-proliferative diabetic retinopathy in one or both eyes (microaneurysms, exudates, and/or small intraretinal haemorrhages). The visual acuities in these patients varied from 20/15 to no worse than 20/40.

Eight patients had advanced retinopathy (proliferative retinopathy, old vitreous haemorrhages, and secondary fibrosis) with visual acuities ranging from hand movements to 20/20.

Each patient underwent a complete ocular examination. The visual fields were examined with a Goldmann perimeter using the appropriate distance and addition for age in plotting the central isopters. The peripheral isopters were plotted with the patient wearing no correction. Before each examination the perimeter was checked for standardization of illumination. When small white targets (1/1, 1/2) showed no defects, red targets were used.

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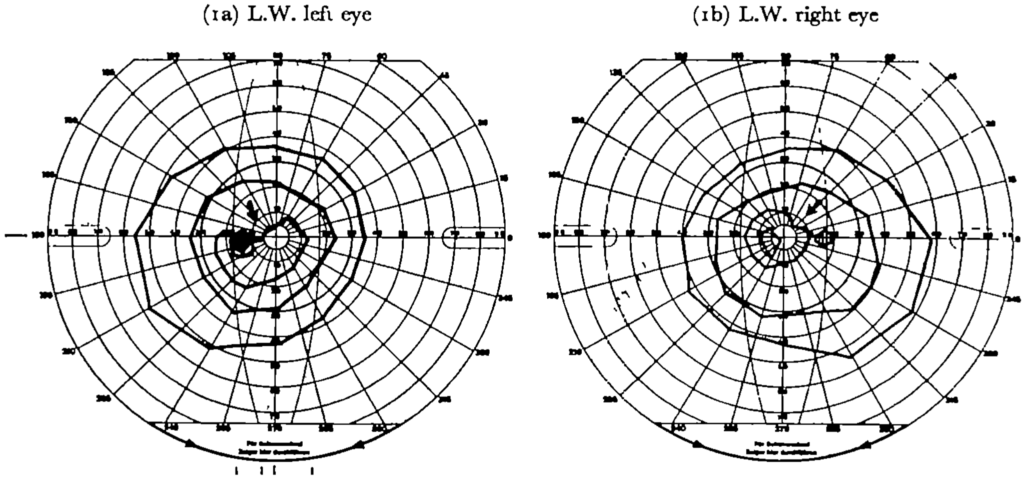
An ophthalmoscopic examination was performed after dilatation of the pupils with phenylephrine (Neo-Synephrine®) 10 per cent. and tropicamide (Mydriacyl®) 1 per cent. Kodachrome fundus photographs were taken using the Zeiss fundus camera. Fluorescein angiography was performed using an intravenous injection of 5 ml. 10 per cent. sodium fluorescein solution.* Kodak Tri-X Pan black-and-white film was used. The fluorescein angiograms corresponding to the visual field defects were enlarged.

All patients with non-proliferative diabetic retinopathy showing significant visual field defects have undergone retesting one or two months after the initial examination. Visual field abnormalities were found to be reproducible.

Results

The three patients without diabetic retinopathy showed no visual field abnormalities.

The group of thirteen patients with non-proliferative retinopathy included six without demonstrable visual field defects and seven (9 eyes) with a similar arcuate-type field defect (Figs 1, 2, 3, and 4). With small targets this abnormality appeared to a be partial constriction of the central isopter. These field defects arose from or close to the blind spot and extended nasally, arching either upwards or downwards towards the macula. It appeared that a slightly larger or brighter test object would have converted the defect into an arcuate scotoma. but arcuate scotomata could not be plotted in this way. Static perimetry showed a slight decrease in the light threshold in the area of the field loss, but responses were variable.


(1a) L.W. left eye

(1b) L.W. right eye

FIG. 1 *Goldmann visual fields from three patients with non-proliferative diabetic retinopathy. Note localized constriction of central isopters arising from or close to the blind spot. Solid lines represent white targets; broken lines represent red targets.*

Although fluorescein angiograms revealed a much more extensive retinopathy than was seen on ophthalmoscopy or on the ordinary fundus photographs (Fig. 2), the printed enlargements of the areas of the fluorescein angiogram which corresponded to the visual field defect did not differ significantly in regard to type or degree of retinopathy from enlargements of retinal areas in the opposite half of the field with normal visual function

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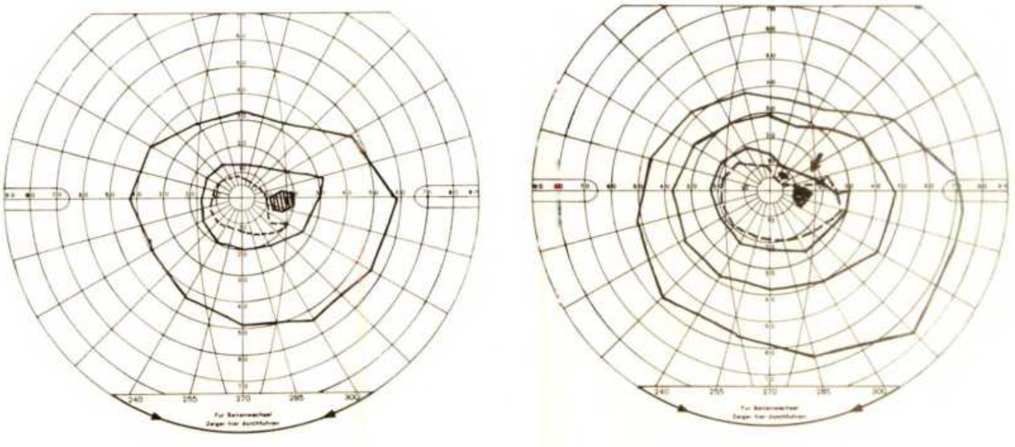
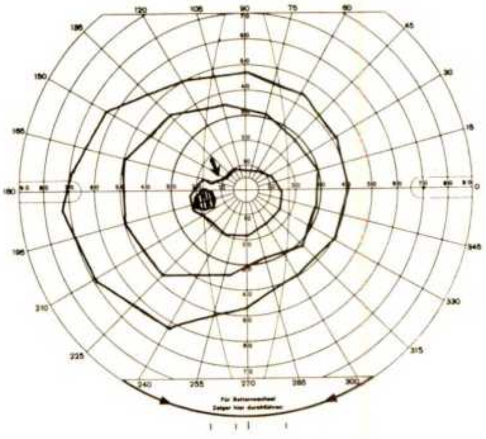
* Fluorescein sodium solution 10 per cent., Smith, Miller and Patch, Inc., New York.


(1c) A.F. right eye

(1d) O.L. right eye

(2a)



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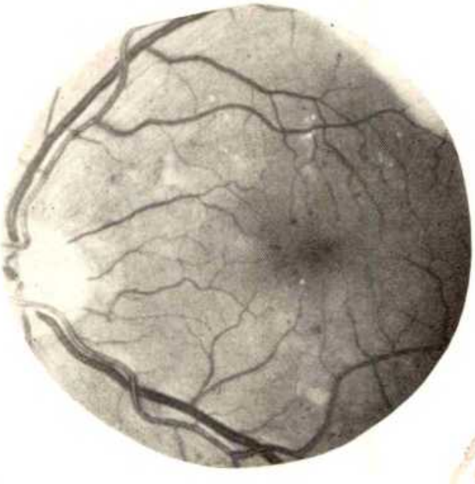

(2c)

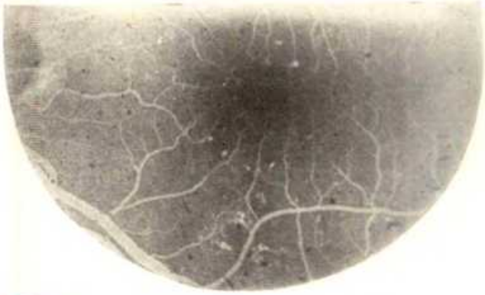

FIG. 2 *Left eye of patient N.L. with non-proliferative retinopathy. The fundus photograph and fluorescein angiogram show no specific vascular lesion infero-temporal to the optic disc which would correspond to the field defect supero-nasal to the blind spot.*

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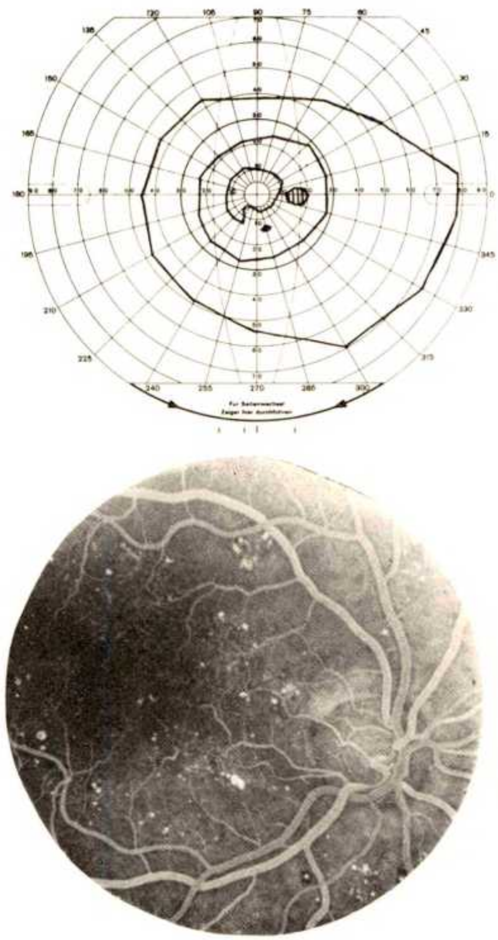

FIG. 3 *Right eye of patient G.S. with non-proliferative retinopathy. The upper and lower areas of the fundus as seen on the fluorescein angiogram show no signficant differences in degree or type of lesion although the superior area is associated with a field defect.*

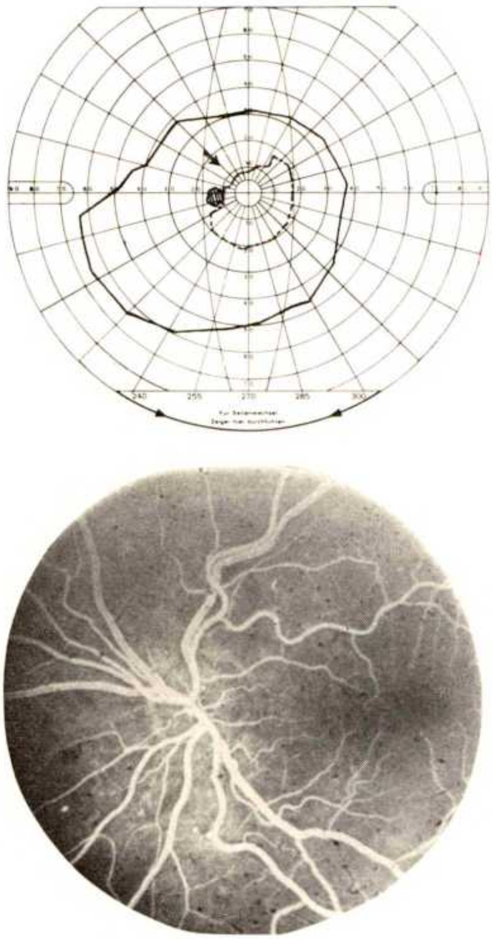

FIG. 4 *Left eye of patient A.F. with non-proliferative retinopathy. The fluorescein angiogram shows no specific vascular lesion corresponding to the visual field defect. Solid line represents white target; broken line represents red target.*

(Fig. 3 and Fig. 4). The seven patients showing these defects had been diagnosed as diabetics for 1, 9, 10, 11, 12, 20, and 24 years respectively.

Seven of the eight patients with advanced proliferative haemorrhagic retinopathy showed visual field defects which were easily explained by the appearance of the diabetic lesions: central scotomata were related to macular haemorrhages and oedema; peripheral visual field defects were associated with large retinal or preretinal haemorrhages, vitreous haemorrhages, and/or areas of fibrous or neovascular lesions in the retina and vitreous; and arcuate scotomata were associated with lesions of retinitis proliferans in contact with the optic disc. The eighth patient of this group had chronic simple glaucoma and showed bilateral scotomata with minimal retinitis proliferans about the macula. It was not possible to tell to what extent the arcuate scotomata were related to the glaucoma or to the diabetic retinopathy.

Discussion

Partial constrictions of the central visual isopters in patients with non-proliferative diabetic retinopathy have not been described previously. It was not possible to determine any specific vascular abnormality associated with this type of visual dysfunction. A vascular lesion responsible for these defects might be beyond the resolution of clinical fluorescein angiography.

The type of defect plotted in patients with non-proliferative diabetic retinopathy shows some similarities to the arcuate scotoma of glaucoma. However, all patients showing this type of defect had normal optic discs and the intraocular pressures recorded in this group were normal. One current theory suggests that abnormalities in the radial peripapillary capillaries might be responsible for arcuate scotomata in glaucoma (Henkind, 1967; Kornzweig, Eliasoph, and Feldstein, 1968). With the present method of fluorescein angiography, detailed photographs of the radial peripapillary capillary network are not usually obtained but, as seen in Fig. 5, the location of this capillary system makes its involvement suspect in the particular type of defect found in this study. It is of interest that new vessels arising from the disc usually follow the pathway of the radial peripapillary capillaries.

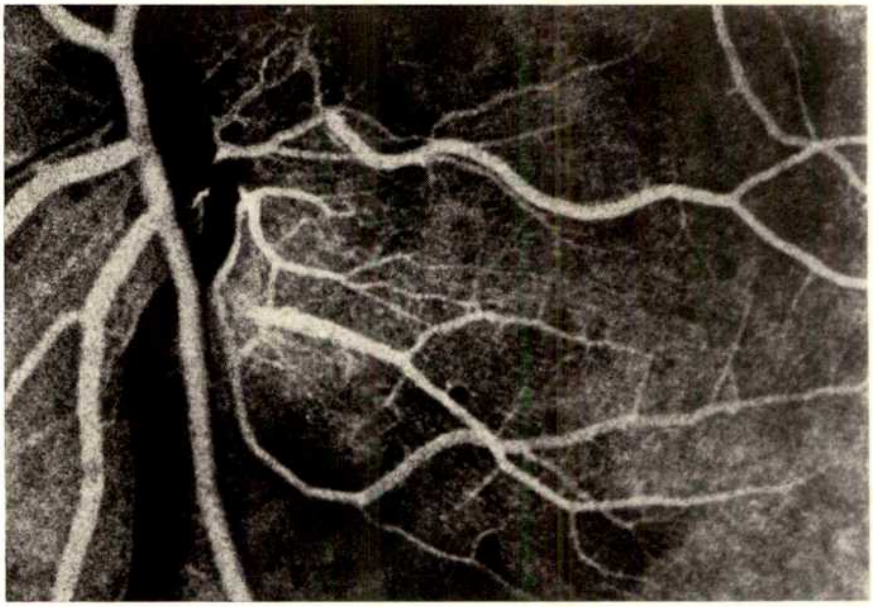

FIG. 5 *Arterial phase of normal fluorescein angiogram, showing straight radial peripapillary capillaries arising from the infero-temporal border of the disc.*

A non-vascular metabolic defect within the nerve fibre layer could be responsible for visual field abnormalities. All of the above explanations are conjectural. There is not as yet convincing clinical or investigative evidence favouring any one of these possibilities.

Since the arcuate field defect may be a precursor to proliferative vascular changes, patients showing this defect will continue to be examined periodically.

Summary

Visual field defects in the form of partial constriction of the central isopters were found and studied in diabetic patients with non-proliferative diabetic retinopathy.

We thank Mr. Donald Wong and Miss Muriel Laban for the photography throughout the investigation. We also thank Drs. Henry Dolger and Stanley Mirsky for referring patients for the study.

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Live trachoma vaccine and topical therapy

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It was stated (Scott, 1964) that a live trachoma vaccine had no clear-cut effect in cases of severe trachoma although there were encouraging results in patients with mild trachoma and in a volunteer. This paper, which describes a further study supported by statistical analysis carried out on 553 children over a period of 5 years, confirms that no clear-cut benefit was obtained from the use of a live trachoma vaccine in cases of severe trachoma.

Material and methods

A school for 300 native Bantu children aged from 7 to 15 years was selected in the Northern Transvaal where classical trachoma was known to be common. Attendance at school was not compulsory and only 193 were present at the first examination in 1965 by Scott and Pienaar, who reached agreement on their findings, each using a loupe in daylight. Pannus of 2 to 3 mm. and Herbert's pits were found in 48 of the first fifty children examined, after which these signs were ignored. The upper lid was everted and three abnormal signs were commonly found.:

(1) Follicles

(2) Hyperaemia

(3) Hyperplasia of the tarsal conjunctiva.

These were not necessarily regarded as signs of trachoma but each was given a figure to represent severity as described later by the statistician. Of the 193 children, 113 had signs of active infection, nineteen had scars in a quiet eye, and 41 had a normal tarsal conjunctiva.

In the following 3 years, the new intakes of 111, 126 and 123 children were examined and the old cases re-examined by the same two ophthalmologists. Swabs for TRIC culture were positive in 91 of 98 unselected children in 1965; this high proportion of positives fell to 55, 28, and 8 per cent. in the three successive intakes although the incidence of trachoma and the average point score were much the same in each group. Cultures were done by Mrs. Cuthbertson and Miss Ryan at the South African Institute for Medical Research.

Another curious feature was that a higher proportion of positive cultures came from those with lower total scores (*e.g.* 3, 2, or 1). In each intake there were one or two carriers, *i.e.* patients with a normal tarsal conjunctiva who yielded TRIC agent on culture but had a total score of 0.

A live trachoma vaccine (E.I.D. 10^{-3}), prepared at the South African Institute for Medical Research under the direction of Prof. J. H. S. Gear, was given by subcutaneous injection to one-third of the children selected by random numbers. Each vaccinated child was given a second dose a month later and a booster dose each subsequent year. If a patient was absent when the vaccinations took place, every effort was made to give the vaccine at the earliest opportunity and nearly all of the selected children received their quota of vaccine. There was only one case of reaction (allergic oedema). As practically every child in that area contracted trachoma by the age of 1 year it was decided to treat all scholars (irrespective of initial score) with 1 per cent. tetracycline ointment once daily during their first school year in the hope that the vaccine would prevent reinfection when treatment was stopped.

A total of 552 children was examined and 184 were given vaccine. An analysis of the results is given below. The response to therapy will be the subject of another communication.

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Statistical report on the findings

There are two basic groups of patients: those who received the vaccine and those who did not.

Each child was examined from time to time and the severity of each of three signs was noted on a four-point scale: 0, 1, 2, 3. The sum of these three scores, which can vary from 0 to 9, is taken as an overall indication of the severity of the disease at a given time. Two typical results are shown in Table I. If observations are missing, it was not possible to find the child on a given date for re-examination.

Table I *Results in two patients, one with vaccine and one without*

Vaccine	*Patient no.*	*Date examined and total score* 1965 *Feb.*	1965 *Jun.*	1965 *Oct.*	1966 *Jan.*	1966 *Sept.*	1967 *Feb.*	1968 *Feb.*	1969 *Feb.*	1969 *Sept.*
Given	68	3	1	4	3	0	2	2	–	1
Not given	61	3	0	2	3	–	3	1	2	1

Each of the two basic groups was divided into subgroups, according to their initial total score (0 or 1 . . . or 9) and the date when this was obtained. For each subgroup the average score at each date of re-examination was computed.

A typical result (for initial score 3 and initial date Feb., 1965) is given in Table II and the Figure, for those who received the vaccine and those who did not.

Table II *Average scores with and without vaccine*

Date examined	1965 *Feb.*	1965 *Jun.*	1965 *Oct.*	1966 *Jan.*	1966 *Sept.*	1967 *Feb.*	1968 *Feb.*	1969 *Feb.*	1969 *Sept.*
$\bar{x}$: WITH *vaccine*	3	1·22	2·00	1·44	0·55	2·50	1·43	1·00	1·50
No. examined	10	9	9	9	9	8	7	1	4
S.D. of $\bar{x}$		0·22	0·60	0·11	0·34	0·94	0·39	?	0·57
$\bar{y}$: WITHOUT *vaccine*	3	0·86	2·28	2·22	0·43	1·44	1·16	2·00	2·20
No. examined	12	7	7	9	7	9	6	1	5
S.D. of $\bar{y}$		0·55	0·66	0·81	0·14	0·29	0·39	?	1·06
$\bar{x}-\bar{y}$	0	+·36	−·28	−·78	+·12	+1.06	+·27	−1·0	−·70
S.D. of $\bar{x}-\bar{y}$		0·60	0·89	0·81	0·38	0·98	0·56	?	1·2

These two subgroups are logically comparable. When comparing them, either from the table or from the graphs, one would like to see that the mean scores for those vaccinated are smaller than the scores for those not vaccinated, and to see these differences steadily increase as time goes on. This would be evidence that the vaccine helps. But the differences vary in an erratic manner. Furthermore, the estimated standard deviations of the individual differences are so large that no sound statistical evidence exists for judging whether or not any particular "true" difference is positive or negative.

Many such comparable pairs of subgroups exist and their mean scores were tabulated and graphed. In all cases the two graphs intertwined erratically in much the same way as in the Figure.

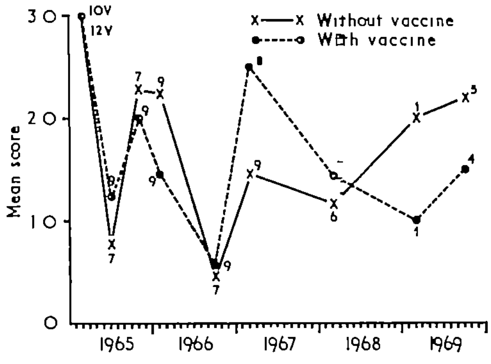

FIGURE *Typical result. See Table II*

The disadvantage of having so many comparable pairs of subgroups is that the number of observations in each is small. But any method that can be evolved for combining these subgroups into two large subgroups and comparing them, with the idea of using a statistically more powerful test of the effects of vaccination, necessitates making various assumptions before the comparison can be regarded as valid. These assumptions we are not prepared to make.

In conclusion, then, with the evidence arranged in Tables such as Table II, our judgement is that the vaccine did not help the patients at all.

Clinical and laboratory studies were supported by a grant from the South African National Council for the Blind. Grateful thanks are expressed to the Council and to the two technicians Mrs. Cuthbertson and Miss Ryan.

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Brit. J. Ophthal. (1971) 55, 192

Retinal vascular occlusion as a presenting feature of glaucoma simplex

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The purpose of this study has been to assess the frequency with which chronic simple glaucoma presents in an outpatient clinic as some type of retinal accident and also the significance of the association.

Although it is generally accepted that a thrombotic glaucoma can complicate a central retinal venous occlusion, the frequency of retinal venous occlusion occurring in eyes with established glaucoma simplex seems less well known, even though this was first described by Verhoeff (1913) and has been emphasized by Duke-Elder and Jay (1969). Some recent authors (Becker and Post, 1951; Higgitt, 1956; Dryden, 1965; Tarkkanen, Raitta, and Vannas, 1967) have mentioned the relationship between simple glaucoma and central retinal venous occlusion, although Raitta (1965) postulated that tributary venous occlusion was no commoner in simple glaucoma than in comparable age groups of the general population.

It seemed to us that it would be useful to assess the extent of this relationship of simple glaucoma to retinal vascular occlusion using the improved diagnostic methods now available, especially applanation tonometry and electronic tonography.

Aetiology of retinal vascular occlusion in glaucoma

The factors contributing to retinal vascular occlusion have been discussed by Duke-Elder and Dobree (1967); these include defective arterial flow, stagnation of the circulation, degenerative and inflammatory vascular disease, and glaucoma. It is most likely that glaucoma acts by producing circulatory stagnation as demonstrated by Moses (1963) in studies on the relationship of intraocular pressure to vascular flow using a hydrodynamic model eye. Moses showed that the flattening of the rubber tube (the vessel) was at first localized to the "venous" end, but that, as the "intraocular" pressure was increased further, the flattening extended towards the "arterial" end. It is therefore also likely that in the human eye glaucoma would affect the area of the central retinal vein, where vascular pressure is lowest.

However, since the incidence of both vascular disease and glaucoma simplex increase with age, it is probable that vascular changes also participate in the aetiology of occlusion.

Methods of present study

The clinical material of this study consisted of the patients referred to the glaucoma clinic of this hospital for investigation following a retinal vascular accident during the period 1967 to 1969. Of the 727 patients referred during this period, glaucoma was not confirmed in 86.

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Address for reprints: Wolverhampton and Midland Counties Eye Infirmary

The intraocular pressure was measured by a Goldmann applanation tonometer on the 900 slit lamp, and this is also the routine method used in the outpatient clinics. The tonography was performed using a Schwartzer electronic tonometer and recorder, the results being processed by an ICT 1500 computer at the Birmingham Regional Board by a method previously reported (Woodhouse, 1969).

Clinical details and results

Of the 727 patients referred, 25 had had a retinal vascular occlusion and the clinical details of twenty with confirmed glaucoma are summarized in Table I. It should be noted that in five patients with a vascular occlusion glaucoma was not confirmed, and that two patients had had bilateral venous occlusion at the onset of their symptoms. All patients had open drainage angles.

Table I *Clinical details of twenty patients with confirmed glaucoma in the eye affected by vascular occlusion*

Type of retinal vascular occlusion (with confirmed glaucoma)	*Number of patients*		*Average values for each group*			
	Male	*Female*	*Age (yrs)*	*Intraocular pressure*	*Outflow facility* (C_e)	*P/c*
Central vein	10	5	60	28	0·22	127
Tributary vein	3	1	62	24	0·17	140
Central artery	1		50	22	0·10	220

Table II shows the incidence of glaucoma in relation to the total number of patients attending with retinal vascular accidents and indicates the visual results after treatment.

Table II *Incidence of glaucoma and retinal vascular occlusion in 3 years*

Type of retinal vascular occlusion	*New patients attending hospital during 3 years*			*Treatment of cases referred*		*Visual result (acuity, field)*		
	Total with a retinal vascular occlusion	*Total referred to glaucoma clinic*	*Total eyes with glaucoma*	*Total eyes controlled (pressure < 21 mm.Hg)*	*Total with anti-coagulants*	*Improved*	*No significant change*	*Deteriorated*
Central vein	64	20	15	11	6	4	9	2
Tributary vein	35	4	5	4	1	3	2	
Central artery	40	1	1	1		1		
TOTAL	139	25	21	16	7	8	11	2

Discussion of the results of 3-year survey

(1) DIAGNOSIS

The diagnosis of glaucoma in retinal venous occlusion may be easily missed if the possibility of glaucoma is not suspected, as the increase in intraocular pressure is often small. In our series the average intraocular pressure was 27 mm.Hg when first measured (range 17 to 50). However, tonography has been useful in the diagnosis of borderline cases and the average coefficient of facility of aqueous outflow (Ce) was 0·2 mm.^{3}/min./mm as compared with 0·38 for eyes in which glaucoma had been excluded.

The importance of the examination of the contralateral eye must be stressed, since failure to diagnose glaucoma in this eye may lead to loss of visual function either through a second vascular occlusion or through progressive glaucomatous optic atrophy. In our series fifteen patients had evidence of glaucoma in the contralateral eye, and nine of these showed a higher intraocular pressure in this eye than in that with vascular occlusion at the first attendance. It seems probable that the intraocular pressure of the eye affected by retinal venous occlusion is more unstable, and this has been confirmed by repeated measurements of the pressure (applanation phasing).

(2) INCIDENCE AND AETIOLOGICAL FACTORS

Of the 641 patients attending with a confirmed diagnosis of chronic simple glaucoma, twenty (3·1 per cent.) had presented with an acute visual disturbance due to a retinal vascular accident. Although this is only a small percentage of the total group of glaucoma patients, it does represent 14·4 per cent. of the total group of retinal vascular occlusions attending during the same period. If venous occlusions are considered separately, the percentage rises to 25 per cent. for central vein occlusion, but falls to 8·6 per cent. for tributary vein occlusion. It would therefore seem that glaucoma is a significant feature in the aetiology of venous occlusion, and we would advise the investigation of every case for glaucoma, including a routine applanation tonometry of both eyes at the first visit.

The incidence of primary glaucoma in this series (25 per cent. for central vein occlusion and 8·6 per cent. for tributary vein occlusion) is fairly close to estimates in previous series. Raitta (1965) examined 258 patients with retinal venous occlusion occurring over a period of 14 years and reported an incidence of 28 per cent. for central vein occlusion, but commented that the incidence of glaucoma in tributary vein occlusion was equivalent to that in the general population aged 65 years and over. However, in our series, fourteen of the twenty patients were less than 65 years old. Dryden (1965) showed an incidence of glaucoma in 19 per cent. of eyes with central vein occlusion and in 69 per cent. for the opposite eyes; this study was partly histological, which may have produced a higher incidence of advanced cases.

There was a preponderance of males in our series (13 out of 20), which reflects the higher incidence of vascular disease in males.

(3) TREATMENT

The routine treatment for retinal venous occlusion has been anticoagulation, using drugs such as warfarin or phenindione, but this treatment has often proved unsuccessful and is also not without dangers of internal haemorrhage, especially in the older patient. In the present series anticoagulants were given only to the younger patients and those with an occlusion affecting a large area of the retina; those who were treated with anticoagulants did not progress significantly better and, out of six, two retained a visual acuity of less than 6/60, two improved, and two with an acuity of better than 6/12 retained it.

Of those patients with confirmed glaucoma in the eye affected by vascular occlusion (20 in the present series), fourteen were controlled by treatment with miotic eye drops, and acetazolamide as necessary, and two with surgery. In these patients the intraocular pressure had remained satisfactory for periods of 1 to 3 years, but the visual acuity and visual field have shown significant improvement in only eight (two of whom had anticoagulants also). Although this is not a dramatic result, we feel that it justifies the careful control of glaucoma in all such cases, since long-term prognosis of neglected glaucoma simplex is so poor, even without retinal vascular occlusion.

Summary

The aetiology, incidence, and treatment of simple glaucoma in retinovascular occlusion are discussed in relation to a clinical series. 25 per cent. of patients with central retinal venous occlusion had glaucoma, but only 8·6 per cent. of those with tributary venous occlusion. It is emphasized that the diagnosis of simple glaucoma should be considered in all patients presenting as a retinal vascular accident.

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Brit. J. Ophthal. (1971) 55, 196

Oculomotor nerve paresis in a case of scleritis

M. S. DAVIES AND A. G. KARSERAS

Moorfields Eye Hospital, London

Case report

A 59-year-old white woman attended the casualty department on September 23, 1968, with a history of increasing pain and swelling of the left side of the face, and redness of the left eye during the previous week. She had suffered from "rheumatism" in her arms for many years, but otherwise had no serious or significant illness until 3 years previously when she had been found to be hypertensive. Since that time she had been treated with Methyl Dopa 250 mg. twice daily.

Examination

The right eye was normal in all respects. The left eye showed some swelling of the lids and periorbital tissues. The sclera was injected, with overlying chemosis, and the eye was very tender to palpation. There was no staining of the corneal epithelium, the stroma was clear, and there were no inflammatory signs in the anterior chamber. The pupils were equal and showed normal reactions. The lens, vitreous, and posterior pole showed no abnormality, and the corrected visual acuity was normal.

Diagnosis

The case was diagnosed as one of scleritis.

Treatment

Topical steroids (Predsol-N) were administered.

Course

When she was next seen 2 days later the pain in the left eye was more intense, and the following day there was an increased oedema of the lids which suggested the possibility of an orbital infection. Treatment was changed to Penicillin-V 500 mg. four times a day.

The next day, 4 days after she was first seen, the pain was much worse. The left eye was extremely tender and the sclera intensely injected, and visual acuity had dropped to 6/18. The eye was slightly proptosed (exophthalmometry 15 mm. right, 19 mm. left) and there was limitation of adduction and elevation. The most striking feature was a complete ptosis; when the lid was raised the pupil was found to be dilated with no reaction to light or convergence, and the patient complained of double vision. The anterior chamber was shallow and showed a faint flare. The vitreous was clear and the intraocular pressure was normal. Fundus examination revealed a peripheral choroidal detachment on the temporal side extending from 2 to 4 o'clock.

She was admitted to hospital where a general physical and neurological examination failed to reveal any other abnormality.

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Address for reprints: M. S. Davies, F.R.C.S., and A. G. Karseras, Moorfields Eye Hospital, High Holborn, London, W.C.1

Laboratory Investigations

Full peripheral blood count,
Erythrocyte sedimentation rate.
Latex test for rheumatoid factor.
Serum proteins.
Immunofluorescence test for antinuclear factor.
Examination for lupus erythematosus cells
Wassermann reaction and Kahn test
Radiological examination of skull, orbit, nasal sinuses, and chest.
Ultra-sound examination of eyeball and orbit.

The results of these investigations were normal except for some evidence of pleural thickening on the chest film, and elevation of the ESR to 32 mm./1st hr.

Further diagnosis and treatment

It was considered that the original diagnosis of scleritis was correct, and treatment was recommenced on the day of admission to hospital with topical steroids; systemic steroids were witheld in view of the evidence of previous pulmonary inflammation on the chest *X*-ray. The penicillin which had been started the day before was discontinued, and no other therapy was given apart from analgesics.

For 48 hours the symptoms and signs remained unchanged, but the following day there was a slight subjective improvement and objectively the external ocular movements became less restricted. The pupil was less dilated and showed a sluggish response to light. Over the next few days the signs gradually regressed, except for the choroidal detachment which extended to involve the entire periphery of the fundus. Six days after admission it was possible to record the external ocular movements on a Hess chart, and 2 days later the ptosis and proptosis were only slight. The visual acuity improved to a normal level, and the pupil reacted briskly although it remained slightly larger than on the right. The annular choroidal detachment persisted, but 2 weeks after the first examination it showed signs of resolution, and the patient was discharged from hospital 3 days later.

Follow-up

When repeated 2 weeks and 1 month later the ESR was found to be normal.

Comment

It is usual to regard scleritis as occurring in two main forms, anterior and posterior. Anterior scleritis usually occurs in young people, and is more common in females than in males. In the most severe cases an annular scleritis may occur in association with extreme pain. Complications are common, including a secondary sclerosing keratitis and an intense uveitis which may predispose to the development of an exudative retinal detachment. An anterior choroidal detachment may occur infrequently. Posterior scleritis is characterized by oedema of the lids, proptosis, and impaired painful mobility of the globe.

There is marked chemosis, but the cornea and anterior segment remain normal, and the vision may be unimpaired except for the awareness of diplopia. There is an inflammatory infiltration within the extrinsic ocular muscles and also within the other orbital tissues, including even the lacrimal gland. Other intraocular complications have been described; vitreous opacities, choroiditis, retrobulbar neuritis, and exudative retinal detachment (Sears, 1964).

It is evident that this case shows some of the features of both anterior and posterior scleritis, but the main interest lies in the presence of the third cranial nerve paresis, which has not been recorded before in this condition. The latter was indicated by the complete ptosis, the fixed dilated pupil, and reduced elevation and adduction.

Summary

A case of scleritis is presented which was complicated by a third cranial nerve paresis: this complication has not been reported before. An annular choroidal detachment was also present. Full investigation failed to reveal the aetiology of the scleritis, which ran a benign course without recourse to systemic steroids.

Our thanks are due to Mr. K. C. Wybar for permission to publish details of his case and for his assistance in the preparation of this paper.

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Brit. J. Ophthal. (1971) **55**, 199

Intraorbital aneurysm of the ophthalmic artery

LOUIS MEYERSON AND S. J. LAZAR

Johannesburg, South Africa

Intraorbital aneurysm of the ophthalmic artery is a very rare condition. Duke-Elder (1952) mentioned seven reports, some of which lack anatomical verification; these were written between 1823 and 1914 when angiographic studies were not available and the verifications when done were *post mortem* studies.

Dempsey (1886) reported a saccular aneurysm of the ophthalmic artery at the back of the globe associated with a fusiform aneurysm of the internal carotid artery. The patient died and these aneurysms were found *post mortem*.

Wheeler and Baker (1964) found three aneurysms of the ophthalmic artery in 57 cases in which angiography was performed for ocular pathological studies. Only one of these was intraorbital.

Di Chiro (1961) stated that aneurysms of the ophthalmic artery were rarely seen. Lombardi (1967), in 370 intracranial aneurysms seen before 1964, found none in the ophthalmic artery. Parkinson, Jain, and Blair-Johnson (1961) were unable to trace previous reports of saccular aneurysms arising from the ophthalmic artery.

Case report

A 55-year-old white man was first seen in 1963, when the external examination of his eyes and ophthalmic investigations were negative apart from presbyopia.

PREVIOUS MEDICAL HISTORY

He had had an injury to the head during the second world war with uneventful recovery. At times he heard "blowing" noises in the head.

FAMILY HISTORY

A brother had died from a ruptured intracranial aneurysm, and the patient's only child had died at birth with a suspected intracranial haemorrhage.

RECENT MEDICAL HISTORY

On November 14, 1968, at 8 a.m. the patient coughed and developed a "haemorrhage and protrusion" of the right eye. An intramuscular injection of pethidine 50 mg. was given by his general practitioner, and he was examined (by L. M.) at 11 a.m. on the same morning.

There was marked proptosis, a large subconjunctival haemorrhage, and a haemorrhage that had suffused into the lids and periorbital tissues (Figs 1 and 2, overleaf). The pupil was fixed and dilated and in the mid-position. There was no perception of light.

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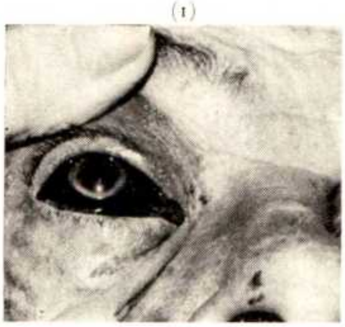
Address for reprints: Dr. Louis Meyerson, 723 Medical Centre, Jeppe Street, Johannesburg, South Africa



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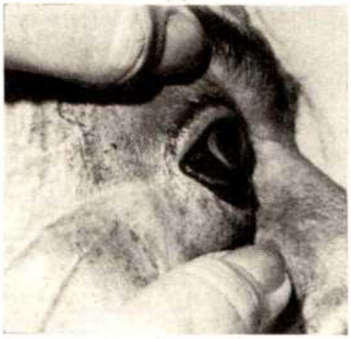

(2)

FIGS 1 and 2 *Pre-operative appearance, showing proptosis, a large subconjunctival heamorrhage, and haemorrhage that has suffused into lids and periorbital tissues*

The patient was admitted to the Brenthurst Clinic and treated with compress bandage and sedatives.

On the same evening the external features remained the same, corneal sensation was lost, and muscle movements were completely absent because of mechanical limitation of the globe. No bruit was heard.

The fundus showed marked dilatation of the larger and smaller retinal veins. There was little change at the macular area.

General physical and neurological examinations were performed by a physician and neurologist on the same day, but there were no significant findings.

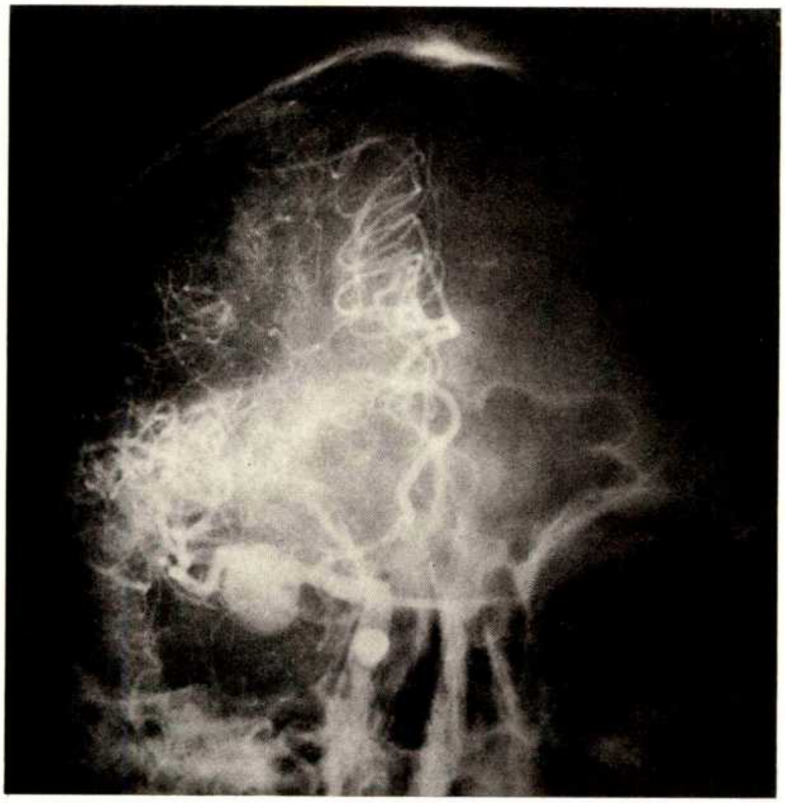

FIG. 3 *Right carotid antero-posterior angiogram, showing intraorbital aneurysm*

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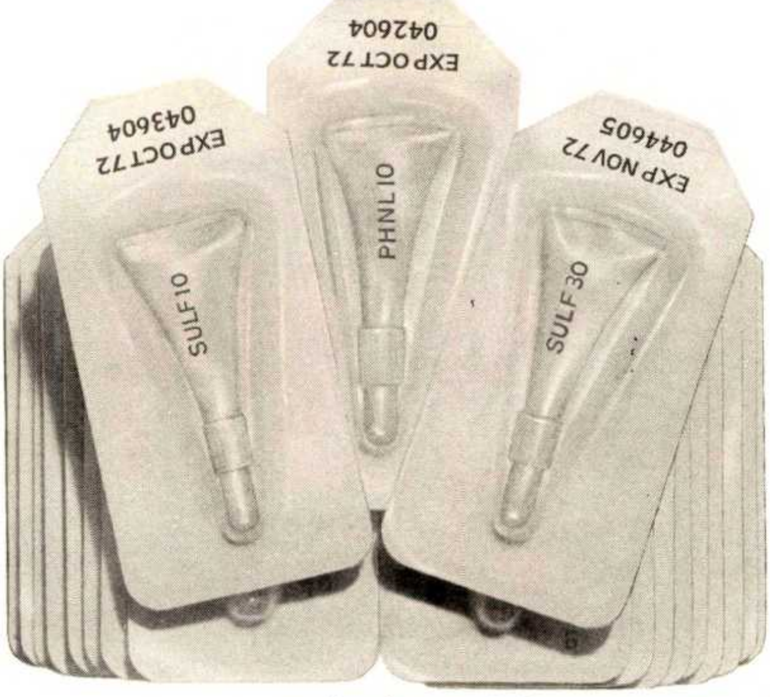

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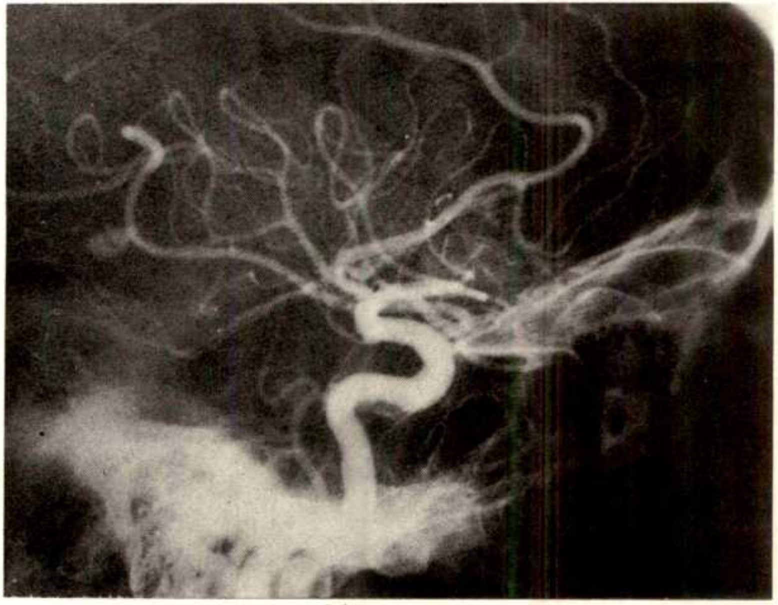
Blood studies (November 15, 1968). Packed cell volume: 44 vol. per cent., Erythrocyte sedimentation rate: 13 mm./1st hr. (Wintrobe) (corrected rate 10 mm./1st hr.). Non-fasting blood sugar: 105. Wassermann reaction: negative Blood count: normal.

Radiology

X ray of the skull, including tomography of the orbits, revealed soft-tissue veiling over the right orbit but no evidence of bone destruction or calcification within the orbit. The optic foramina appeared normal on both sides. Bilateral carotid angiography under local anaesthesia on November 16, revealed a 1·3 cm. retro-ocular aneurysm in the right orbit. An irregular filling defect at the antero-inferior margin of the aneurysm probably represented blood clot. The ophthalmic artery was occluded close to the aneurysm. No other intracranial aneurysms were evident (Figs 3, 4, and 5).

(4)



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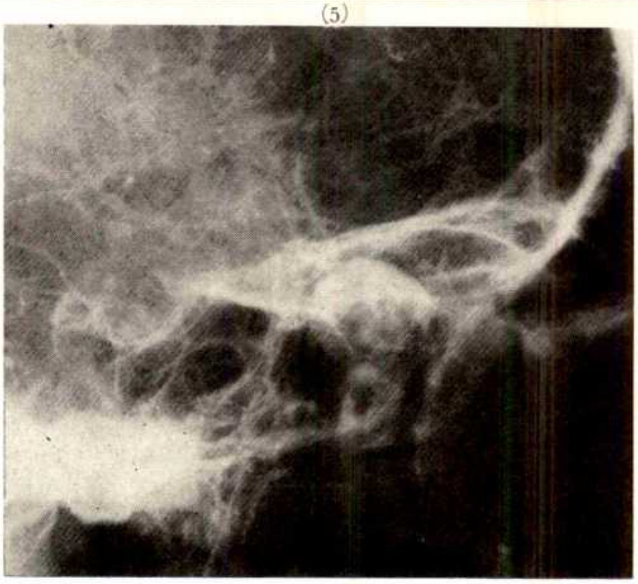


FIGS 4 and 5 *Right lateral carotid angiograms, showing the aneurysm in arterial and venous phases.*

Filling defects antero-inferiorly represent blood clot. The ophthalmic artery is demonstrated and a beaded appearance is noted. The artery tapers close to the aneurysm

DIAGNOSIS

Blood leaking from an intraorbital aneurysm of the ophthalmic artery.

MANAGEMENT

On November 21, a right lateral orbitotomy was performed by Berke's approach. The laternal rectus was reflected and a necrotic black mass was seen to extend between the apex of the orbit and the globe.

An unsuccessful attempt was made to clip the anterior part of the mass, and further blunt dissection with sponges caused a massive haemorrhage, which could not be controlled by manual pressure through towels.

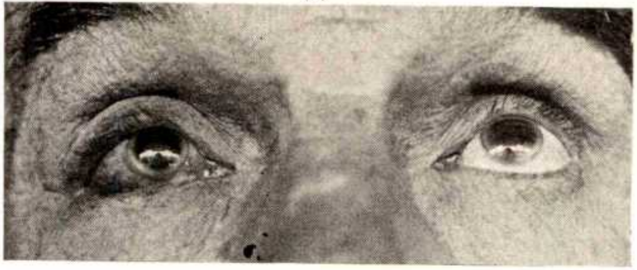
About six haemostats (artery forceps) were then applied to the mass at the apex of the orbit, and by keeping this group of forceps in a particular position, the bleeding was stopped. These forceps were taken off one at a time and it was then realized that the bleeding was being controlled by the pressure exerted by the tip of one forceps at the apex of the orbit. This pressure was maintained and the remnant of the black necrotic mass was dissected away. When the mass had been removed and the pressure of the haemostat at the apex of the orbit (optic foramen) was released there was no further bleeding. The laternal rectus muscle was resutured into position, the lateral part of the orbit was wired into position, and the wound was closed.

A transfusion of 2 pints of blood was given during the operation.

The postoperative period was uneventful. Muscle movements were full in all directions, except for dextroversion in which movement was absent. There was no ptosis and the proptosis resolved within a week (Figs 6 and 7).

Immediately after the operation the fundus showed a pale disc and a cherry-red spot at the macula.

(6)



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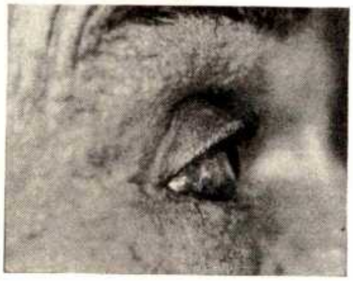


FIGS 6 and 7 *Postoperative appearance, showing resolution of proptosis*

PATHOLOGICAL FINDINGS

No arterial tissue was demonstrated.

POSTOPERATIVE RADIOLOGICAL FINDINGS

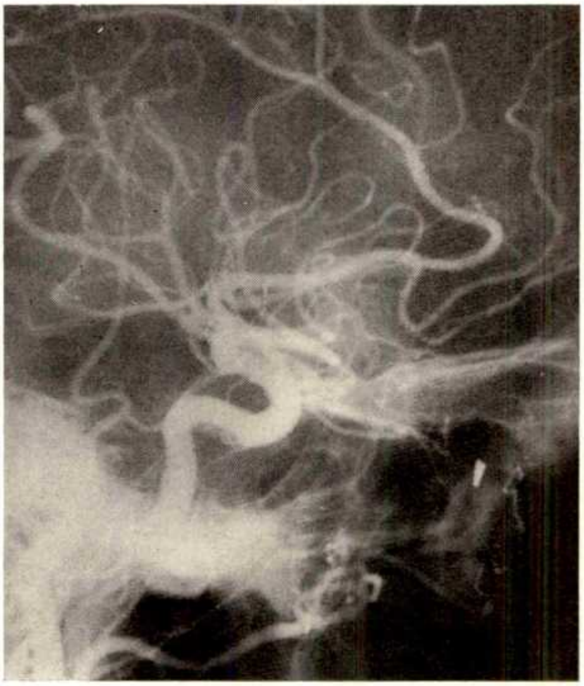
A cerebral angiography on January 10, 1969, under general anaesthesia showed successful obliteration of the aneurysm demonstrated previously. A metallic clip was noted at the site, and two metallic sutures were noted in the lateral wall of the orbit, the fragments of which were in good position. The ophthalmic artery was obliterated in the orbit (Figs 8 and 9).

Comment

A decision had to be made whether this aneurysm should be dealt with by the transfrontal approach or a lateral orbitotomy. The latter was chosen for the following reasons:

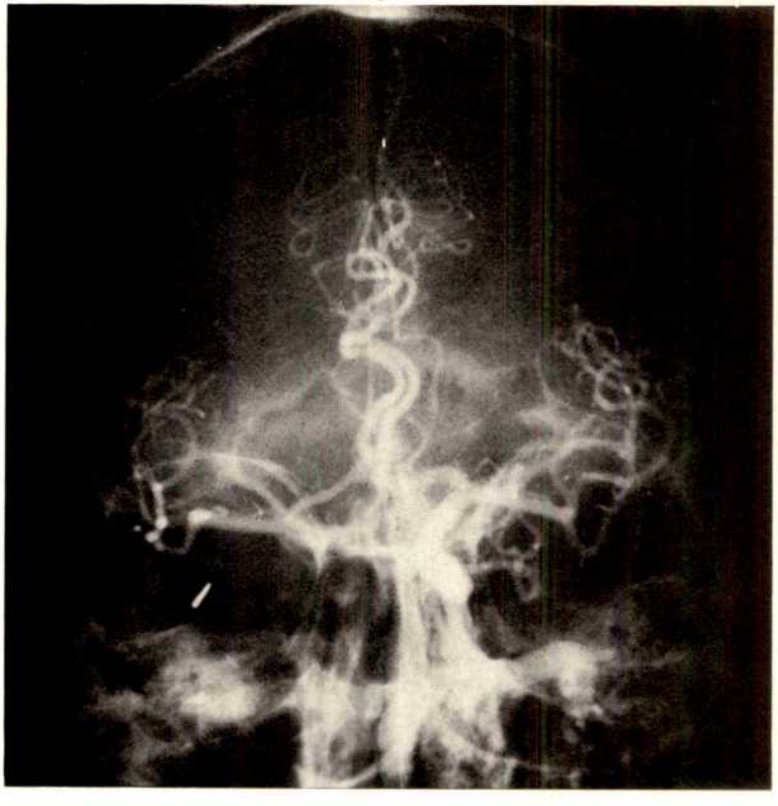
(*a*) The ophthalmic artery enters the orbit below the optic nerve and is rarely located on the medial side of the orbit.

(8)



FIGS 8 and 9 *Postoperative cerebral angiograms, showing successful obliteration of the intraorbital aneurysm of the ophthalmic artery*

(9)



(*b*) In the transfrontal approach, subsequent ptosis and superior rectus weakness can occur. Mortality is high (4·1 per cent.) even in good hands (Stallard, 1964).

(*c*) Excision of the frontal lobe has sometimes been necessary for better access to the orbit (Stallard, 1964).

(*d*) Opening of the frontal and ethmoidal sinuses may lead to meningitis and rhinorrhoea and a stormy postoperative period (Stallard, 1964).

The reason for the massive haemorrhage which occurred during the operation was thought to be the lack of elastic tissue in the wall of the aneurysmal remnant. Thus, when the wall had been disrupted, no contraction took place and the short normal part of the artery had no stimulus to contract and continued to pump blood into the aneurysmal sac.

Had an enucleation been decided upon this complication would still have occurred.

Injury by the haemostats caused the VIth nerve palsy.

The absence of arterial wall tissue in the pathological specimen submitted to section may have been due to the disruptive nature of the preoperative and operative haemorrhages.

Radiologically there was no doubt that this was a ruptured saccular aneurysm of the intraorbital part of the ophthalmic artery and vascular malformations were not considered.

A comprehensive survey of the literature revealed a surprising paucity of cases of intraorbital aneurysm of the ophthalmic artery.

We believe this to be the first case of an aneurysm of the intraorbital part of the ophthalmic artery which has been managed successfully, *i.e.* as far as the life of the patient was concerned and also the preservation of the eye albeit blind.

Summary

A case of a patient who survived the rupture of an intraorbital aneurysm of the ophthalmic artery is presented. The management and radiological features are discussed.

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Brit. J. Ophthal. (1971) **55**, 205

Retinal tear extension through the cryosurgical scar

WILLIAM V. DELANEY, JR.

From the Department of Ophthalmology, State University of New York Upstate Medical Center

The popularity of retinal cryopexy is increasing (Lincoff, McLean, and Nano, 1964). Some workers (Havener and Gloeckner, 1967) indicate that anything less is obsolete. The advantages claimed for it are intact sclera, lower infection rate, and less vitreous damage. Disadvantages include clumsy instruments, risk of choroidal haemorrhage and the difficulty of working with invisible applications.

Shea (1968), however, mentioned the possibility of extension of retinal breaks after cryosurgery. Six of 117 consecutive patients treated prophylactically by the author with cryosurgery had vitreous haemorrhage due to extension of retinal tears. This compares unfavourably with the absence of haemorrhage following photocoagulation for similar disease in 74 patients. The discrepancy warrants attention.

Cryopexy technique

All patients were treated trans-sclerally or transconjunctivally by the Linde or Amoils cryoprobe under observation by the indirect ophthalmoscope (Fig. 1). The margins of each freeze overlapped around the outline of the tear. Additional applications were made at the base of the operculum. A second ring of non-overlapping lesions was placed outside the first and always brought to the ora serrata. Applications on the tear edge were continued until slight whitening of the retina occurred. The second row lesions were limited to freezing the choroid. Treatment of lattice degeneration consisted of coalescent freezing in full-thickness retina around weak areas with a second row of applications peripheral to it. One patient had a scleral imbrication to create a small buckle. None of the patients

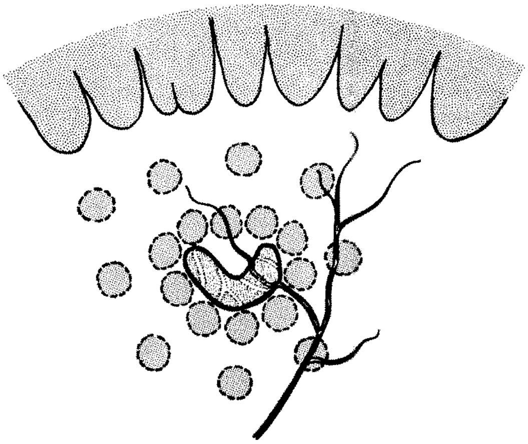

FIG. 1 *Placement of the cryosurgical lesions*

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had frank retinal detachment. All had vitreous haemorrhage and all had tears superior to the long posterior ciliary nerves. All patients achieved a well-pigmented scar around the retinal tear in the expected time and before the subsequent bleeding (Table).

Table *Summary of results in six cases*

Case No.	*Sex*	*Age (yrs)*	*Operation*	*Time of re-bleeding after initial treatment (mths)*	*Additional treatment*	*Final visual acuity*
2	M	65	Trans-conj. cryopexy	2	None	20/20
3	F	51	Trans-conj. cryopexy	8 12 14	Further cryopexy None Diathermy and local buckle	20/30
4	F	57	Trans-conj. cryopexy	4 7 10	Further cryopexy None None	20/40
5	F	65	Trans-conj. cryopexy	4	Local buckle and cryopexy	20/25
6	M	56	Trans-conj. cryopexy	6 (Cataract surgery in interim)	None	20/20
1	M	64	Cryopexy and scleral imbrication	7	Laser photocoagulation	20/20

Summary of case histories

(1) A 64-year-old white male had a surge of "green seaweed" in the right eye 3 months after bilateral cataract surgery. His vision was reduced to 20/50 and a retinal tear was observed at 11.30 o'clock between the ora serrata and the equator (Fig. 2). The retinal edges were elevated and the operculum was vertical in the vitreous. Cryopexy with a scleral imbrication for a local buckle was done. The buckle gradually disappeared, but 7 months later the patient complained of a sudden "cloud" in the same eye. Vitreous blood was again present and an extension of the original tear anteriorly through a well-pigmented cryosurgical scar was shown by small retinal haemorrhages at the margins. No other holes or tears could be found. Laser photocoagulation was used to supplement treatment.

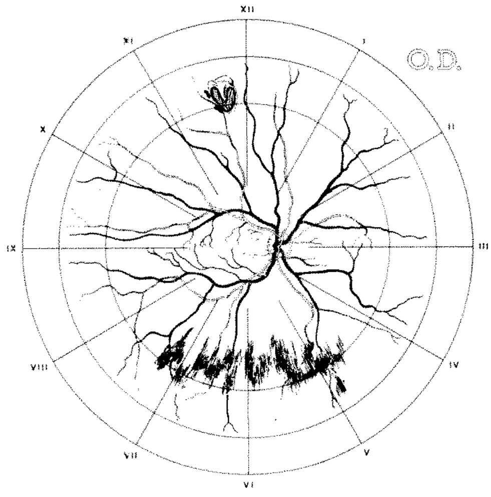

FIG. 2 *Patient* 1

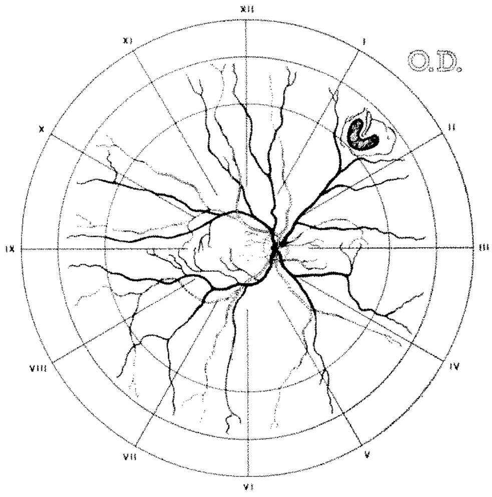

FIG. 3 *Patient* 2

(2) **A 65-year-old white male myope** had extraction of a hypermature cataract and recovered 20/20 vision in the right eye. After 20 months a retinal tear was discovered at 2.30 o'clock near the ora serrata on routine examination (Fig. 3). Transconjunctival cryopexy was done and a good scar was achieved in one week, but 2 months later vitreous haemorrhage reduced vision to 20/60. No other retinal breaks could be found. The original tear appeared to have extended anteriorly but only within the cryosurgically scarred area. No treatment was given. The visual acuity 1 year later was 20/20.

(3) **A 51-year-old white female** had a sudden vitreous haemorrhage in the left eye which reduced vision to 20/400. Multi-level lattice degeneration was present across both superior quadrants of both eyes (Fig. 4). Tears at both ends of the lattice in each eye prompted bilateral transconjunctival cryopexy. The vision returned to 20/30 in the left eye and the right maintained 20/25. After 8 months the patient noted "smoke" in the left eye. The large superior nasal tear had extended anteriorly as indicated by marginal retinal haemorrhages. New retinal breaks were absent. Further cryopexy was placed; 4 months later bleeding recurred from the same area, and 2 months later the episode repeated. 19 months after the original bleeding, diathermy and local buckling were done. One year later the visual acuity was 20/30 and no further bleeding had occurred.

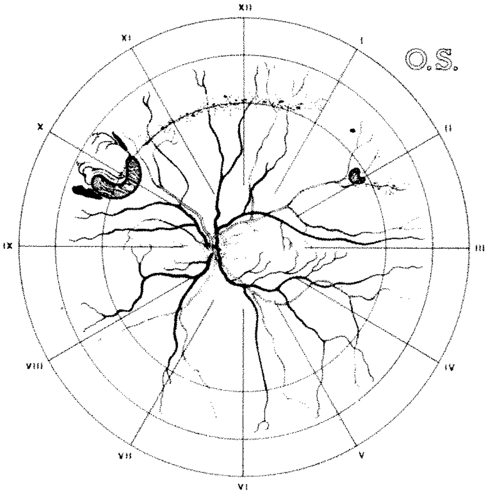

FIG. 4 *Patient* 3

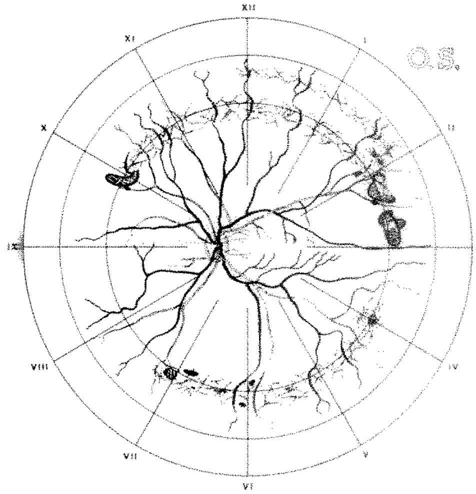

FIG. 5 *Patient* 4

(4) **A 57-year-old white female myope** had had "smoke" in the left eye for 2 months before examination. Vision was 20/20 in both eyes. Multilevel lattice degeneration bridged both superior and inferior quadrants of both eyes (Fig. 5). The left eye had tears at both ends of the superior degeneration. Transconjunctival cryopexy was done, but 4 months later vitreous haemorrhage recurred in the left eye despite coalescent scarring around the retinal breaks and all lattice. More cryopexy was placed, but 3 months later another haemorrhage was associated with obvious extension of the supero-nasal tear. The patient was found to have hypertension and was treated. No new tears occurred and bleeding stopped. No further treatment was given. The retina remained attached 3 months later although the vitreous was hazy.

(5) **A 65-year-old white female** had noted "floaters" for one month before examination. Vision in the right eye was 20/20, and in the left hand movements. Open-angle glaucoma was present in the right eye and the left had a total retinal detachment. The history indicated that the left eye was amblyopic. Surgery improved vision to 20/200. Pilocarpine 1 per cent. controlled the glaucoma in the right eye but 1 month after starting pilocarpine the patient had flashes and a tear was found at 11 o'clock at the equator (Fig. 6). Transconjunctival cryopexy gave good scars; 4 months later a new tear occurred beside the original but within the treatment scars. Slight retinal

elevation prompted the application of further transscleral cryopexy and a trap-door buckle. The vision was 20/25 3 months later.

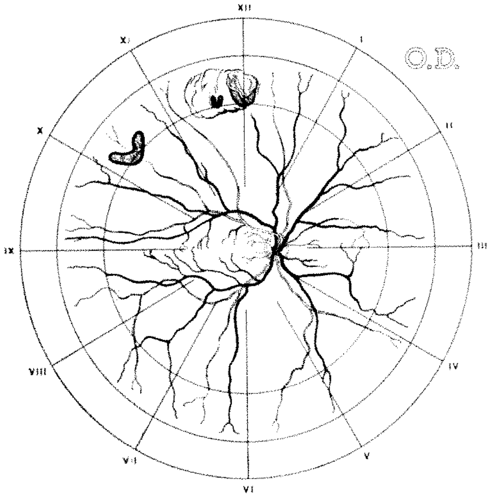

FIG. 6 *Patient* 5

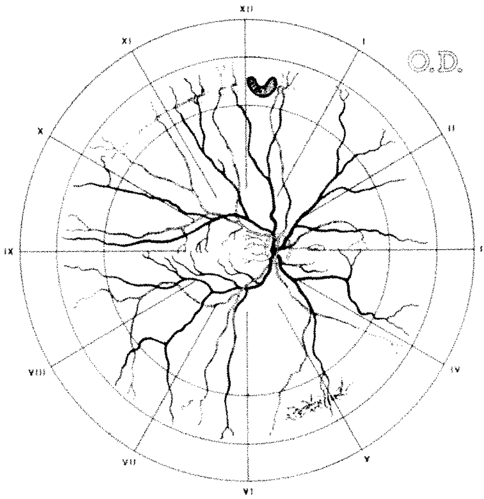

FIG. 7 *Patient* 6

(6) A 56-year-old white male, a mild myope, had had a cataract extraction on the left eye 4½ months before a retinal detachment. Retinal surgery resulted in 20/20 vision. A cataract reduced vision in the right eye to 20/100 3 years later. Before cataract surgery on this eye the patient developed flashes and a small tear was found at 12 o'clock (Fig. 7). Transconjunctival cryopexy was done, followed in 6 months by cataract extraction; 2 weeks after surgery the patient had flashes and only a red reflex could be obtained. The vitreous cleared and the eye was quiet. Expected tears could not be found but small haemorrhages at the margins indicated an extension of the new original tear within the cryosurgical scar. No treatment was given. After 3 months flashes recurred and a new hole was found at 3 o'clock. Laser photocoagulation was used. The vision was 20/20 6 months later.

Results

In six of a series of 117 patients retinal tears extended within visible and well-established cryosurgical scars. All six bled into the vitreous, but none had a retinal detachment, and each retained useful vision. Two had local buckling surgery, one responded to further cryopexy alone, and one to photocoagulation, and two had no additional treatment (Table). Of a further series of 74 patients treated prophylactically with photocoagulation, none had a similar episode.

Discussion

Anatomical facts confirm that vitreous attachment is stronger along retinal blood vessels. Clinical verification comes from the frequent association of vitreous haemorrhage with retinal tears. Almost every tear crosses a blood vessel and four of the six patients presented above demonstrate this fact. In practice, if an operculated tear extends within photocoagulation or diathermy scars, vitreous haemorrhage and retinal detachment are uncommon.

Those who support the use of cryopexy (Lincoff, and others 1964; Lincoff and McLean, 1966; McPherson, 1968) agree that choroidal and retinal blood vessels are spared thrombosis by this procedure. Likewise, Bruch's membrane is left intact (Lincoff and McLean, 1969; Amoils and Honey, 1969). Unlike diathermy and photocoagulation (Kissen,

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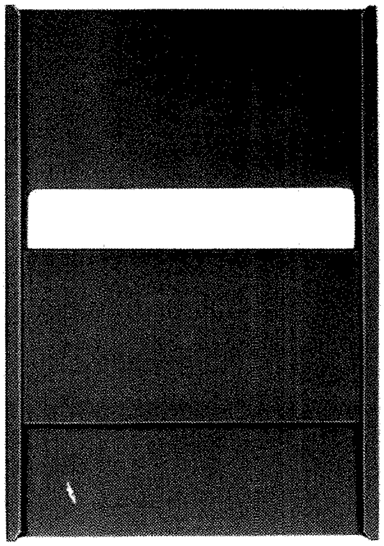

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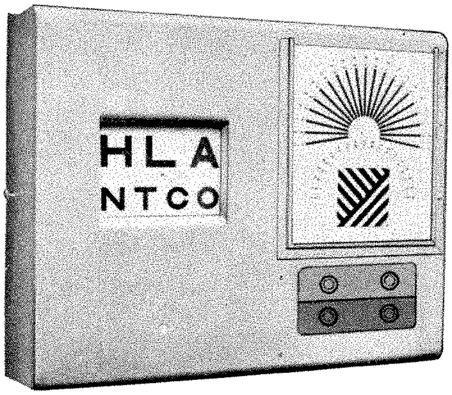

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Delaney, and Wachtel, 1961), this vascular sparing allows contiguous placement of cryosurgical lesions. Despite this metabolic chorio-retinal advantage, intact blood vessels may lead to functional failure from haemorrhage if unrelieved vitreous traction extends the tear.

Accurate knowledge of the tensile strength of heat or cold chorioretinal scars escapes us. Vague ideas exist that increased cold increases strength (Lincoff, Long, Marquardt, and McLean, 1968). If adjacent position, longer duration, and lower temperature can increase lesion strength, the patients herein described show the need for more attention to the hinged edge of a retinal operculum. This adds another reason, apart from accuracy, for visualizing each cryosurgical lesion (Lincoff and McLean, 1969).

Post-operative pain, phthisis, anterior segment necrosis (Duguid, 1967), and implant erosion may follow raised intraocular pressure due to scleral buckling. Large areas of lattice degeneration with multiple retinal breaks often cannot be effectively relieved of traction without risk in the absence of subretinal fluid, even with paracentesis or osmolar therapy to lower the intraocular pressure.

Possible tear extension through the cryosurgical scar makes an indentation reassuring. However, indentations without an encircling element are nearly always externalized and thereby lose their effectiveness in preventing tear extension. The permanency of an encircling element, despite the risk of raised intraocular pressure, must be considered carefully in light of the patients described here if cryotherapy is used.

Transconjunctival cryotherapy for threatening retinal breaks is an advantage not to be ignored. The presence of cataract, vitreous blood, and corneal scars, which prohibit photocoagulation, make it invaluable. While it simplifies the therapy of anterior retinal breaks, it is not a panacea. Those who undertake retinal cryotherapy should be aware of its weaknesses and be prepared to place photocoagulation, a permanent indentation, or diathermy if tear extension through the cryosurgical scar threatens vision with detachment or vitreous blood.

Summary

Six patients are presented who had vitreous haemorrhage due to the extension of retinal tears through well-established cryosurgical scars. All maintained useful vision. Two had supplemental trap-door scleral buckling, one needed further cryopexy, and one responded to photocoagulation. Two had no additional therapy. Awareness of this possible inherent weakness of cryosurgical scars is essential.

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Reversal of the complications of self-induced vitamin A deficiency

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A previous report (Fells and Bors, 1969) has described the case of a 25-year-old man who had deliberately, but illogically, omitted from his diet for 5 years all foods containing vitamin A or the precursor carotenoids, in response to his own idea that vitamin A was responsible for his grand mal epilepsy.

He was observed from the onset of ocular symptoms in March, 1968, to July, 1969, during which time he consistently refused to take vitamin A systemically or even locally. In this interval he developed progressive bilateral corneal xerosis and stromal vascularization, conjunctival xerosis, and severe retinal damage with yellow spots in the fundus (Fig. 1, opposite), great restriction of visual fields, virtually no light-induced rise on electro-oculography and a small residual cone response only in the electroretinogram. Serum vitamin A and carotenoid levels were consistently lower than have been recorded previously in man (Table I).

Table I *Blood levels of vitamin A and carotenoids*

Date	*Carotenoids (µg./100 ml.)*	*Vitamin A (i.u./100 ml.)*
8.5.68		13
29.7.68	13	25·8
30.9.68	3·9	13·6
21.1.69	5	21
12.5.69	3·6	21
10.7.69	0	33
24.7.69	4·8	115
29.9.69	6.0	174
2.2.70	13	190

Normal levels in blood:
100 µg. per cent. carotenoids
150 i.u. per cent. vitamin A

In April, 1969, he developed bilateral, paracentral, interpalpebral, shallow corneal ulcers. Although his visual acuity deteriorated and he was warned of the risk of corneal perforation he declined treatment.

He was admitted to hospital as an emergency 11 weeks later having been bedridden for 3 weeks with an intermittent pyrexia, increasing motor weakness, anorexia, and severe abdominal pain. For 10 days the visual acuity of the right eye had been very poor and the left eye was deteriorating rapidly. He was obviously very ill, with a peculiar greyish-coloured skin and follicular hyperkeratosis and extensive bilateral mid-stromal corneal

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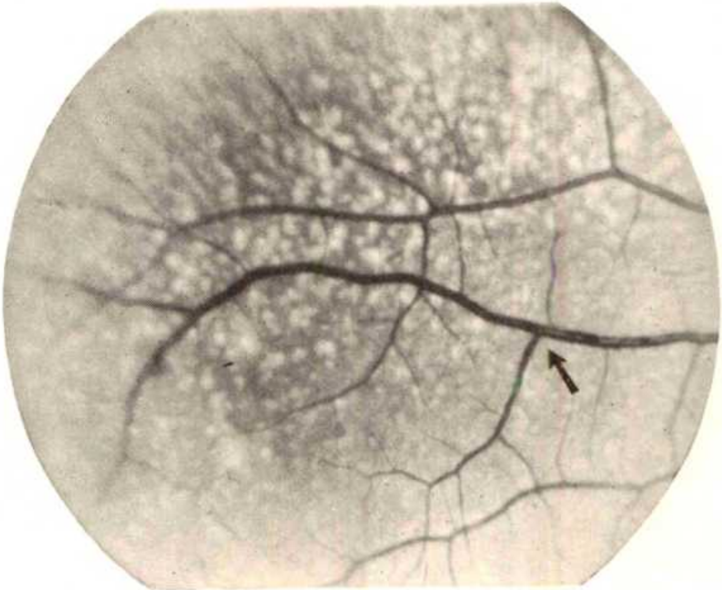

FIG. 1 *Yellow fundus dots before treatment. Arrow marks same vessel in Figs 1 and 3*

vascularization extending to a half-depth interpalpebral ulcer with very little infiltrate in the right eye (Fig. 2). There was no uveitis and vision was light perception in the right eye and 4/60 in the left.

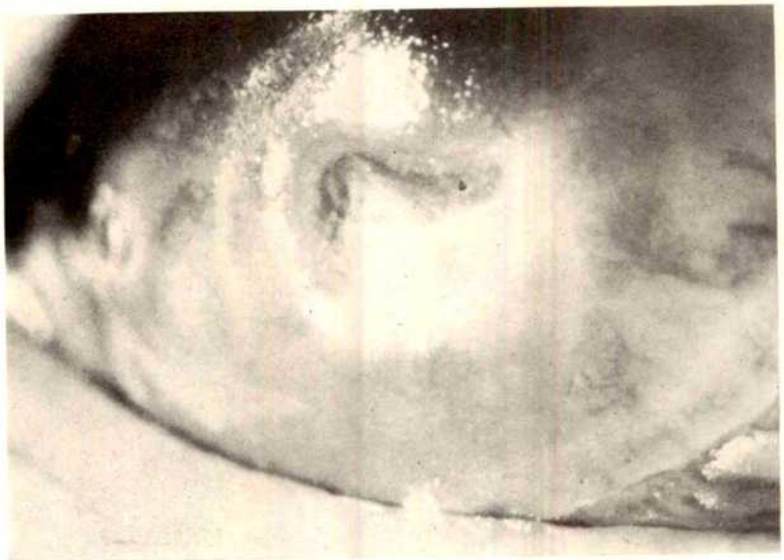

FIG. 2 *Right cornea before treatment, showing vascularization and ulceration*

He finally agreed to have vitamin A therapy which was supervised by Prof. C. E. Dent. Initially vitamin A eyedrops (150,000 i.u./ml.) were given 2-hrly for 2 days with a symptomatic response of less photobia, pain, and watering. He was then given 200,000 i.u. vitamin A intramuscularly followed by vitamin A and D capsules orally four times a day (4,500 i.u. vitamin A, 500 i.u. vitamin D per capsule).

For the next 4 days he had a fever up to 103°F., severe abdominal pain, and anorexia. Despite intensive investigation no cause was found and repeated electroencephalograms were normal except for theta and delta high voltage waves on hyperventilation.

There was a dramatic ocular improvement; within 4 days the right corneal ulcer had decreased to half the original size and the intracorneal vessels were less dilated with closure of some loops. The "crocodile skin" conjunctival pattern had almost disappeared and the eyes were virtually asymptomatic. After 7 weeks only ghost vessels with a little cellular flow remained and the vision had improved to 6/24 in the right eye and 6/5 in the left.

Electrodiagnostic tests were performed before and after treatment. The results (Table II) show a very marked improvement with only a small residual disability. It had been feared that these retinal functions were irreversibly lost.

Table II *Electrodiagnostic tests before and after treatment*

Eye			*Right*	*Left*
Electro-oculogram	Light-induced rise (per cent.)			
	Before treatment		Not detected	Not detected
	After treatment of	: 7 wks	133	114
		11 mths	130	150
Electroretinogram	Before treatment		Not recordable	Not recordable
	After treatment of 7 wks:			
	Photopic response		Within normal limits	
	Scotopic response		b wave slightly small with double top	
	After treatment of 11 mths:			
	Scotopic a wave (μv.)	: 5 min.	40	30
		10 min.	100	100
	Scotopic b wave (μv.)	: 5 min.	90	220
		10 min.	210	210
	Flicker fusion (c.p.s.)		40	40
Dark adaptation	Before treatment		Grossly abnormal both rod and cone sectors	
	After 11 months		Down to 1 log unit at 25 min.	

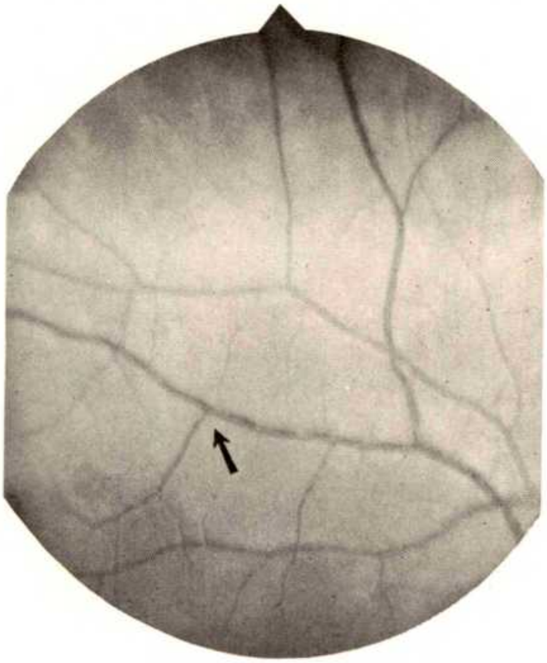

FIG. 3 *Similar area of fundus 5 months after treatment started. Arrow marks same vessel in Figs 1 and 3*

The yellow fundus dots decreased in size and disappeared after 3 months' treatment (Fig. 3), at which time visual acuity was 6/9 in the right eye and 6/5 in the left.

The patient continued the same dose of vitamins A and D for 4 months and then reduced the dose to two capsules per day.

When last seen he was feeling well with normal texture and colour of the skin, inactive corneal scarring, and fine intracorneal ghost vessels. The fundi appeared normal. He has maintained his strange diet which accounts for the persistently low level of serum carotenoids despite normal vitamin A levels. The external appearance of the eye is shown in Fig. 4.

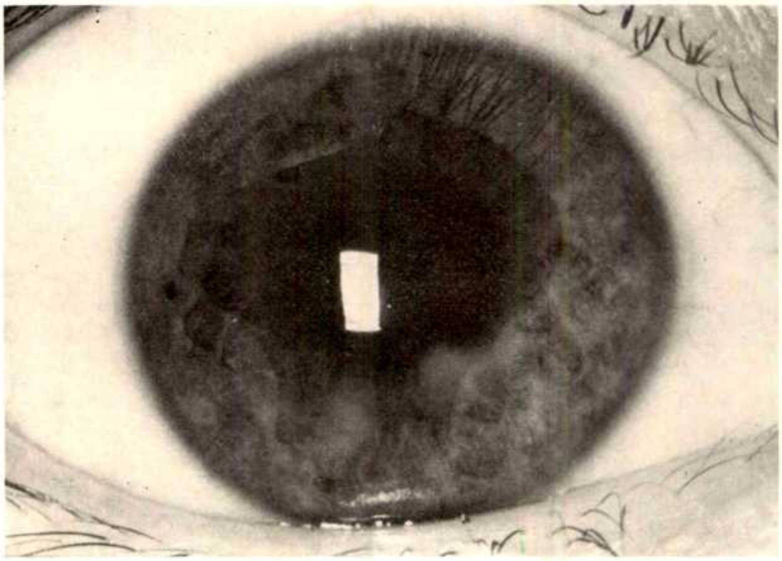

FIG. 4 *Right eye 5 months after treatment*

Discussion

Several features of this case are apparently unique.

The mechanism of the production of the deficiency was extraordinary: a deliberate and successful attempt to eliminate carotenoids and vitamin A from the diet for 5½ years in a country in which a routine diet provides these in abundance.

The very low levels of serum vitamin A have not been previously reported (Sharman, 1969). In the Medical Research Council trial (Hume and Krebs, 1949), restriction of intake to less than 70 i.u. vitamin A per day in sixteen subjects with normal commencing levels resulted in a drop to a minimum level of 20 i.u. per cent. after 24 months in only one subject, the other levels being higher. The only clinical ocular change in those subjects was a mild change in dark adaptation in a few.

The ocular lesions were severe but only very slowly progressive through prexerosis, xerosis and vascularization, and only late corneal ulceration which did not advance rapidly and destructively and was not accompanied by uveitis. This is at variance with the descriptions given of keratomalacia by Sweet and K'ang (1935) and Duke-Elder (1965). However, the epidermal features of this patient were similar to other descriptions, and correspond to the experimental results reported by Fell (1960) in which, in organ cultures of embryonic skin, deficiency of vitamin A induces keratinization of epithelium of mucous type.

The mechanism of action of vitamin A is unknown, but it is known to retard the maturation of cells of the prickle cell layer of the epidermis and the formation of keratin. Excess of vitamin A causes some disruption of fatty protein cell membranes (Fell, 1963).

The acute illness following initial therapy is not similar to that previously reported in nondeprived subjects given massive doses of vitamin A. Reports by Moore (1957) and Oliver and Havener (1958) describe nausea, headache and vomiting, vertigo, diplopia, and papilloedema, presumably all due to a rise in cerebrospinal fluid pressure. The cause of the illness in this patient remains speculative. The recovery of ocular function has been remarkable. Only fine corneal stromal scars remain with retinal function within normal limits (Table II), after very severe damage before treatment.

Previous reports of the treatment of established cases of severe vitamin A deficiency with reversal of the ocular deficiency features were reviewed by McLaren (1963), who emphasized the need for urgent treatment with preformed trans-vitamin A systemically, and felt from the available evidence that there was no precise upper limit to the dose. He suggested a regime of 100,000 i.u./day initially then 30,000 i.u./day to the stage of full healing.

Toxicity from treatment is reported by many observers and can be acute or chronic. The acute features have been noted; the chronic effects were initially described in a child by Josephs (1944) and later by Oliver and Havener (1958) and others. They include the insidious onset of hepatomegaly, painful migrating bone and joint swelling, papilloedema, and ocular palsies. The dose to produce this in adults is probably 100,000 i.u./day for 1 to 2 years. So far this patient has shown no toxic effects on a much lower dose.

Summary

A patient with very severe vitamin A deficiency was observed before and after treatment. The progression and regression of the ocular features are noted.

We are indebted to Prof. C. E. Dent, Dr. T. Moore, and Dr. I. Sharman for the general treatment and investigations, to Dr. G. B. Arden for electrodiagnostic investigations, and to the Department of Audio-Visual Communications of the Institute of Ophthalmology for the photographs.

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Book review

The World through Blunted Sight. By PATRICK TREVOR-ROPER. 1970. Pp. 191, 112 figs. Thames and Hudson, London. (*£4 4s. 0d.*)

The immediate merit of this immaculately produced volume lies in its appeal to the worlds of science and of creative art. Trevor-Roper introduces the subject by tracing the evolution of the visual senses and stressing the major importance of the eye in the sensory hierarchy. This applies not only to the interpretation of environment but also to the expression of personality through a picture or a written word. It is this intermediary role of vision, whether transferring that which is seen to the mind, or the mental image to paper, that is considered in this book. A variety of eye defects is considered, including myopia, hypermetropia, presbyopia, astigmatism, colour blindness, cataract, squint, and glaucoma. Indirect cerebral effects, such as thrombosis, tumours, and schizophrenia, as well as the effects of hallucinatory drugs, are added for completeness; this adds considerably to the value of the book, but it is a pity that the title does not hint at their inclusion. Indeed, the whole gamut from normal vision to total blindness (as well as the complications of making the return voyage) are dealt with most thoroughly. Of necessity, perhaps, this gives an impression of slight imbalance, as the relative importance of these aspects varies considerably. However, each section is sprinkled liberally with delightful anecdotes and facts of historical or mythological interest so any unease is soon dispelled by the sheer enjoyment of reading.

The first half of the book is the most significant from the standpoint of convincing the reader that certain characteristics seen in paintings may be rationally explained in terms of defects in the eye *per se*. These sections are devoted to aberrations in the shape of the eye and abnormal colour vision. The contrast between the intellectual myopic child and the physical hypermetrope is fascinating, and the significance of the former condition in the impressionist school of painting is convincing. It is perhaps a little unkind, however, to hint at an analogy between the impressionists and the "lazy or immature child"!

It is very difficult in a work of this type to avoid the pitfalls of attributing every artistic deviation from the norm to some inherent defect in the eye or mind of the creator. It is commendable that, in general, the author manages to do so. He accepts, for example, that certain shapes and colours may be currently in vogue, the ideas often being distilled from other artists. The attenuation characteristic of El Greco's paintings was probably artificially superimposed for aesthetic reasons, and not attributable to astigmatism and so on. A disadvantage of this liberal attitude is that the reader is occasionally left confused and uncertain as to the final conclusions.

The section on astigmatism provides ample material for a parlour game. The question posed is whether astigmatism in the artist will result in unnatural elongation in one plane of the picture. When drawing from life this would not occur since any abberration in the mental image will be reversed on return to canvas. It has been suggested, on the other hand, that drawing from memory would produce abnormal elongation. The obvious argument against this is that the stored "memory image" of the astigmat will already be elongated, and thus on transfer to paper will again be corrected. I am not happy about Trevor-Roper's slender evidence suggesting the *possibility* of attenuation through astigmatism. He points out that if an astigmatic lens is placed before a normal eye, any attempt to draw a circle from memory will inevitably result in an oval. But this is because the memory image of the normal is indeed a circle, whereas that of the true astigmat is an oval. In the former, therefore, it is a "one-way" process with no compensatory correction. It is also possible that a similar reversal process would invalidate the theory that cataract might produce a preponderance of reddish tones.

There is an obvious but interesting section on the effects of colour blindness, particularly the resort to rather pallid, insipid colours in an attempt to mask their inadequacy. Chapter 4 discusses squint and eye dominance. This is largely of academic interest and is I think the least interesting of the six chapters. The remainder of the book makes fascinating reading, but encompasses a variety of circumstances, cerebral or visual, which affect the personality or the creative art. The final chapter, for example contains a delightful essay relating sight and sex, in the best Freudian manner, as well as some interesting observations on the effect on the personality of a blind man who is allowed to see again. Rather irrelevant in some ways, but as with the whole book, very enjoyable.

Trevor-Roper, with commendable modesty, avoids over indulgence in his own theories, and presents an excellent critical analysis of those of others. A tremendous amount of background research has gone into this unique volume, and every section is entertainingly provocative. The standard of the illustrations is high, and the general lay-out and print appropriately clear. No basic knowledge is required before reading this book, each condition being simply explained, and thus it should have a very wide appeal.

A final point. A curious fact that emerges is that in many cases the artist with defective vision is reluctant to use artificial aids to enable him to see normally. There must be a moral. As an amateur artist myself, my only complaint about this book, is that a minor visual defect of my own does not evidence itself in the same inspired manner as those numerous examples cited in the text.

Note

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Study Tour, 1970

A party of fifteen British ophthalmic registrars began a 12-day tour of Ophthalmic Clinics in Germany and Switzerland on September 5. The programme had a particular bias towards centres specially interested in detachment surgery and culminated in attendance at a meeting of the Gonin Club.

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The party then moved to Essen where we visited Prof. Meyer-Schwickerath in his beautiful new department at the University Eye Clinic. The resources and imagination poured into the building are most impressive, the whole creation being enhanced by an elaborate display of modern paintings and prints.

A full programme of discussions, operating sessions, and demonstrations had been arranged and this was combined with a full social programme, including a visit to see the impressionist paintings at the Museum Folkwang and most generous hospitality from Prof. Meyer-Schwickerath.

After two busy days in Essen, the scene changed to Zürich, where Prof. Witmer and his colleagues had arranged an equally full timetable, including theatre sessions, lectures on such wide-ranging subjects as the aetiology of uveitis, microsurgery, pharmacology of the intra-ocular muscles, and detachment techniques, and an interesting review of fluorescein in photography.

An excursion to the factory at Schaffhausen of Grieshaber, the famous ophthalmic instrument makers, was arranged for us. Here we were given a fascinating display of craftsmanship and most generous hospitality by Herr Grieshaber.

An eventful week came to a close with a delightful evening spent at the home of Prof. and Mrs. Witmer.

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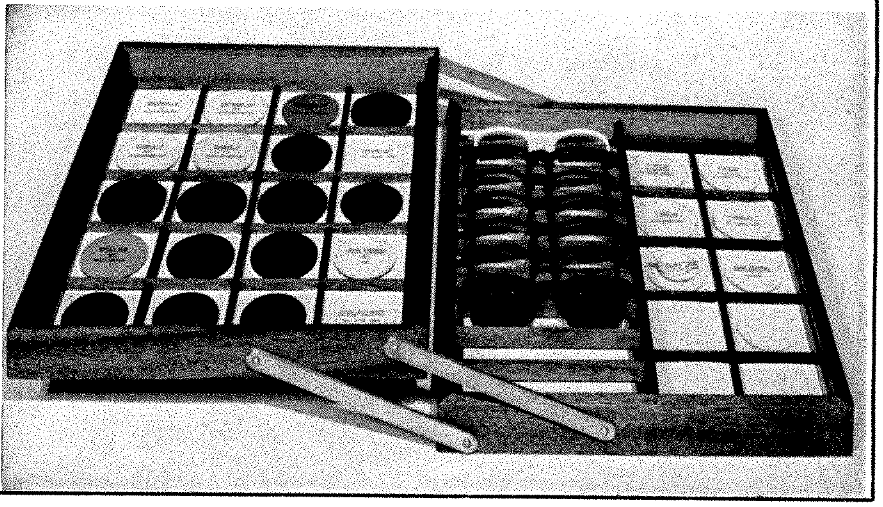

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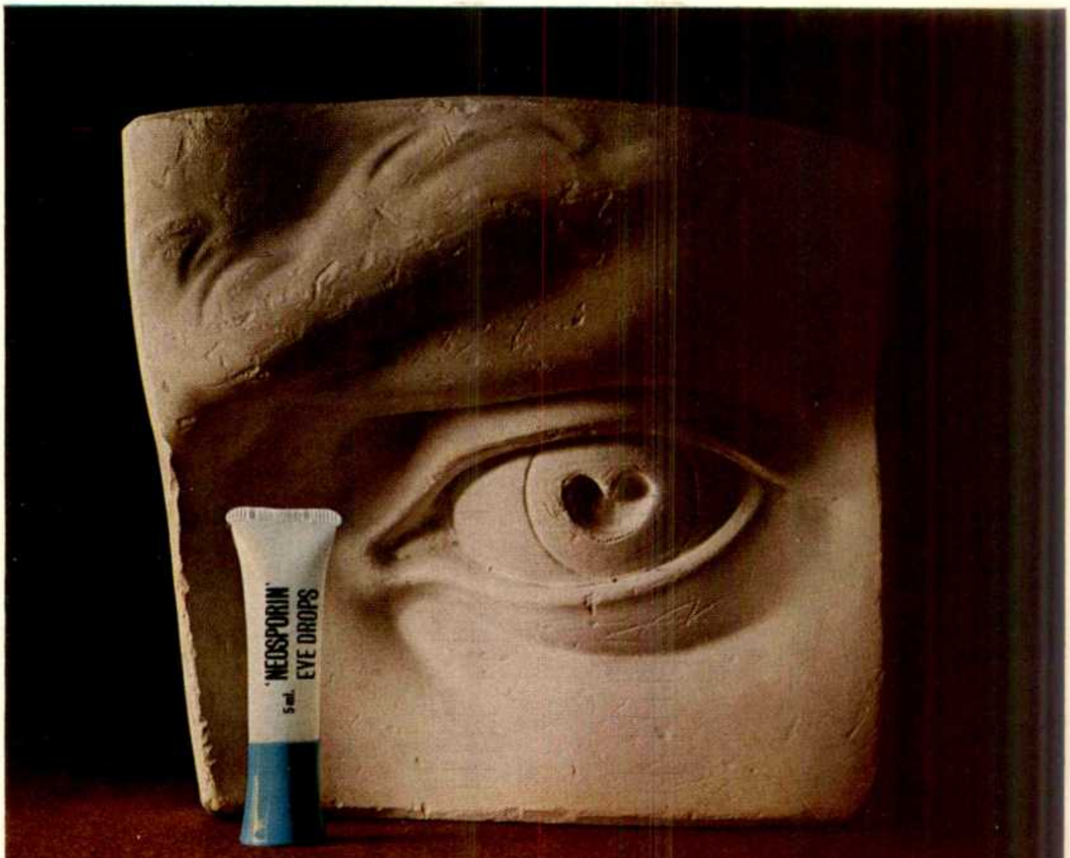

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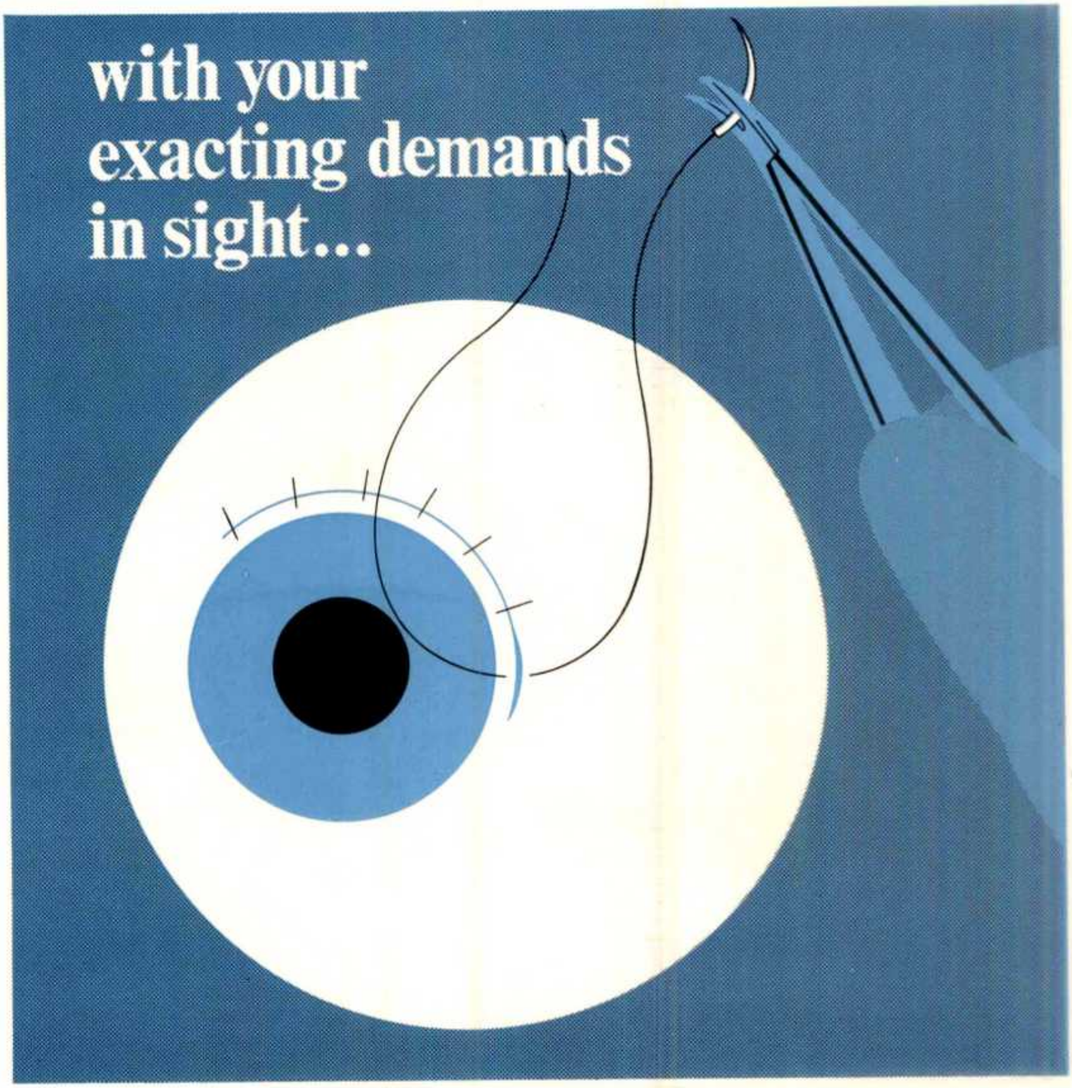

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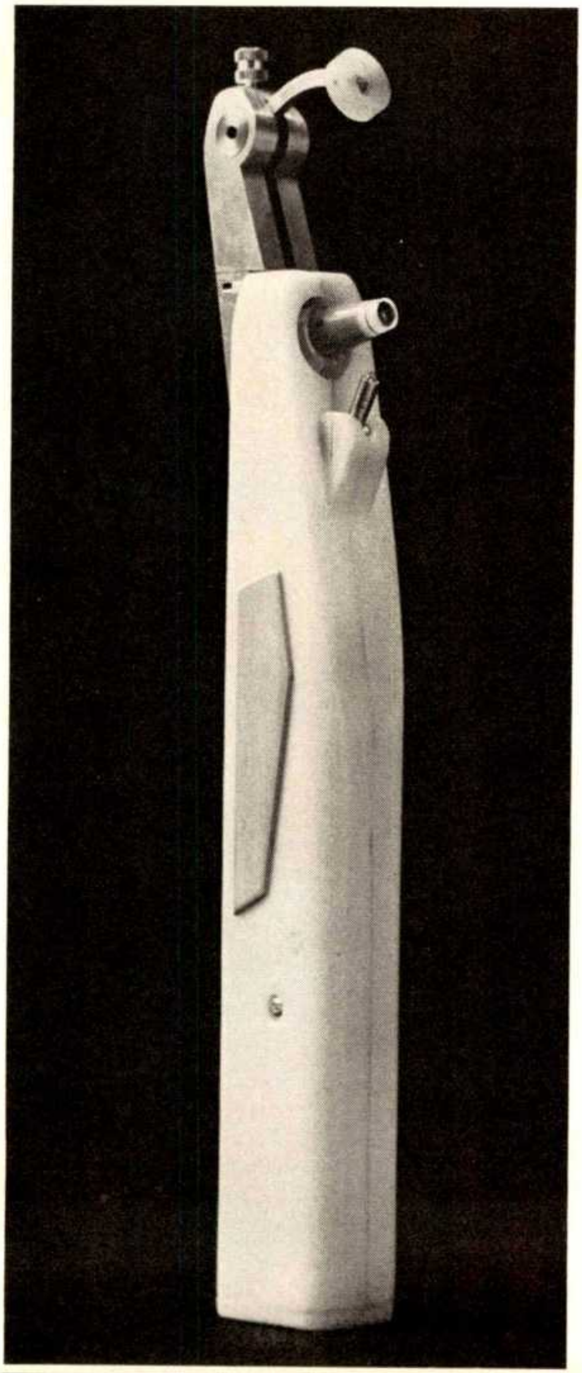

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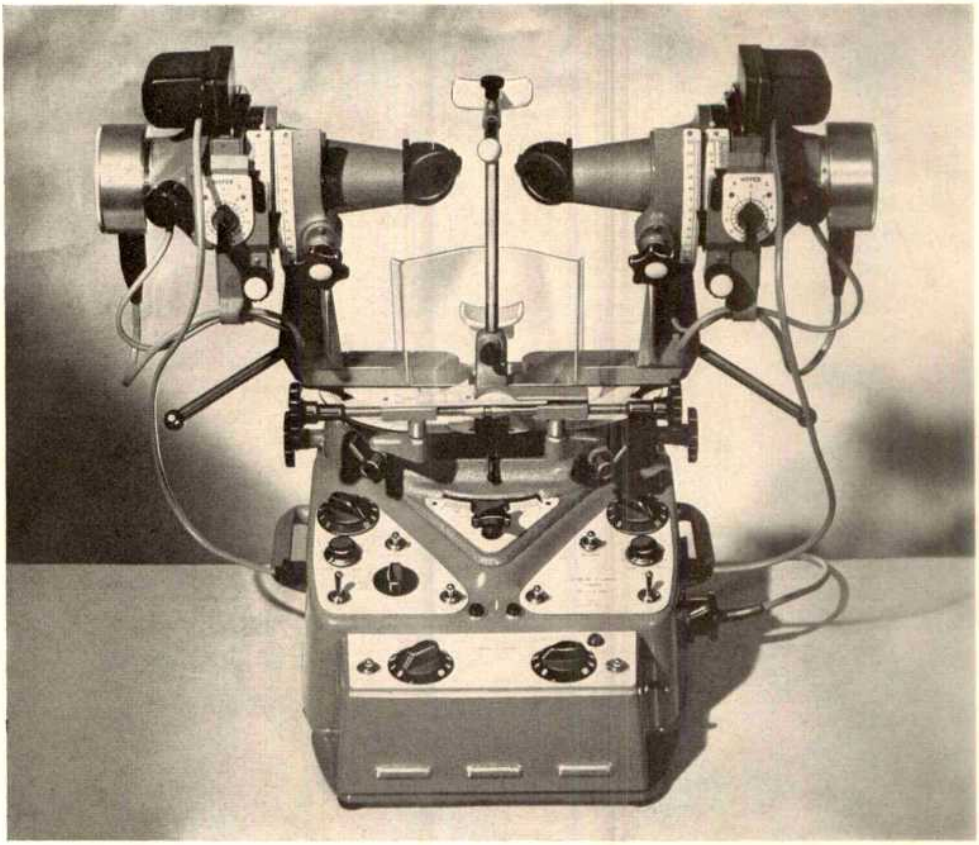

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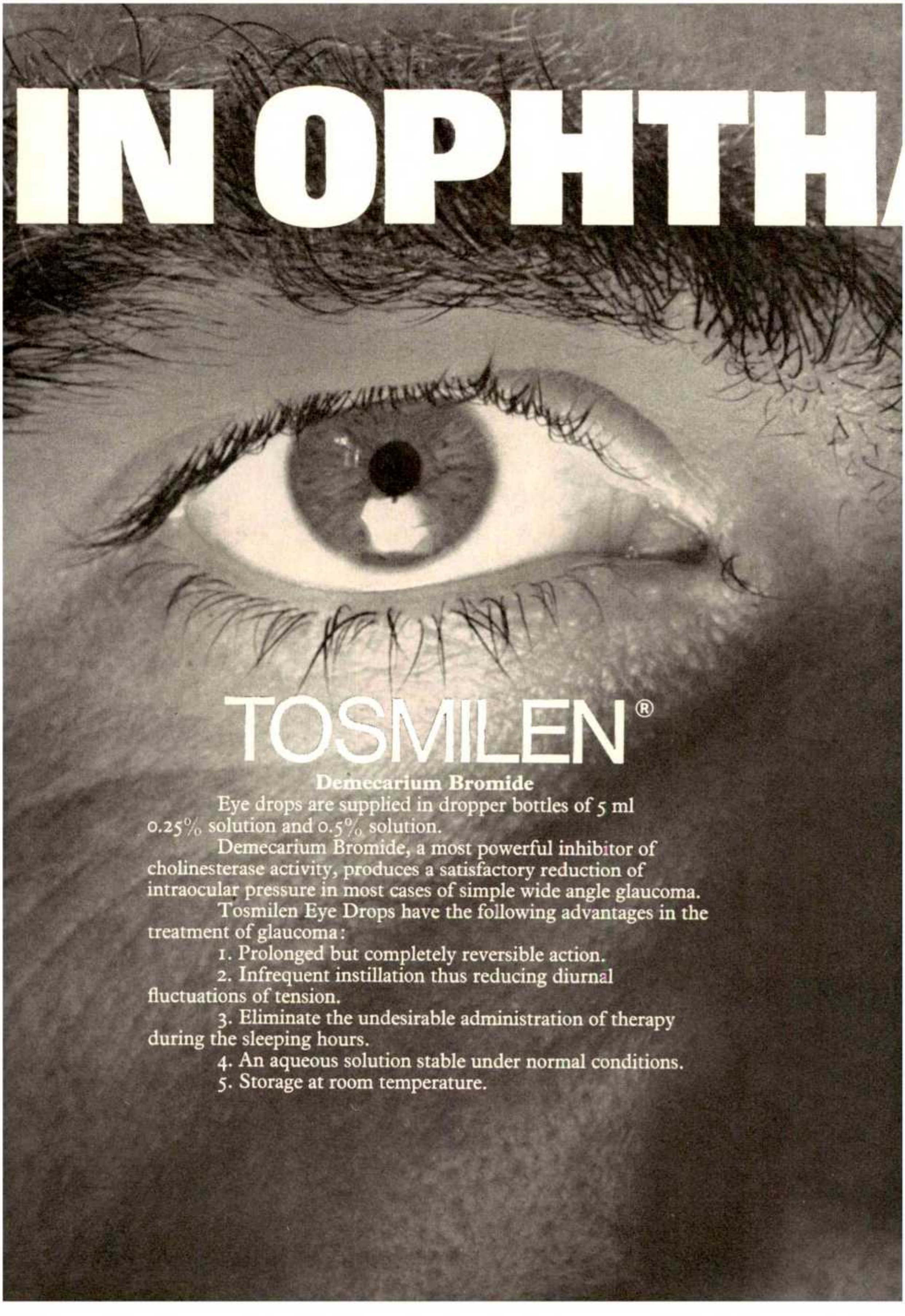

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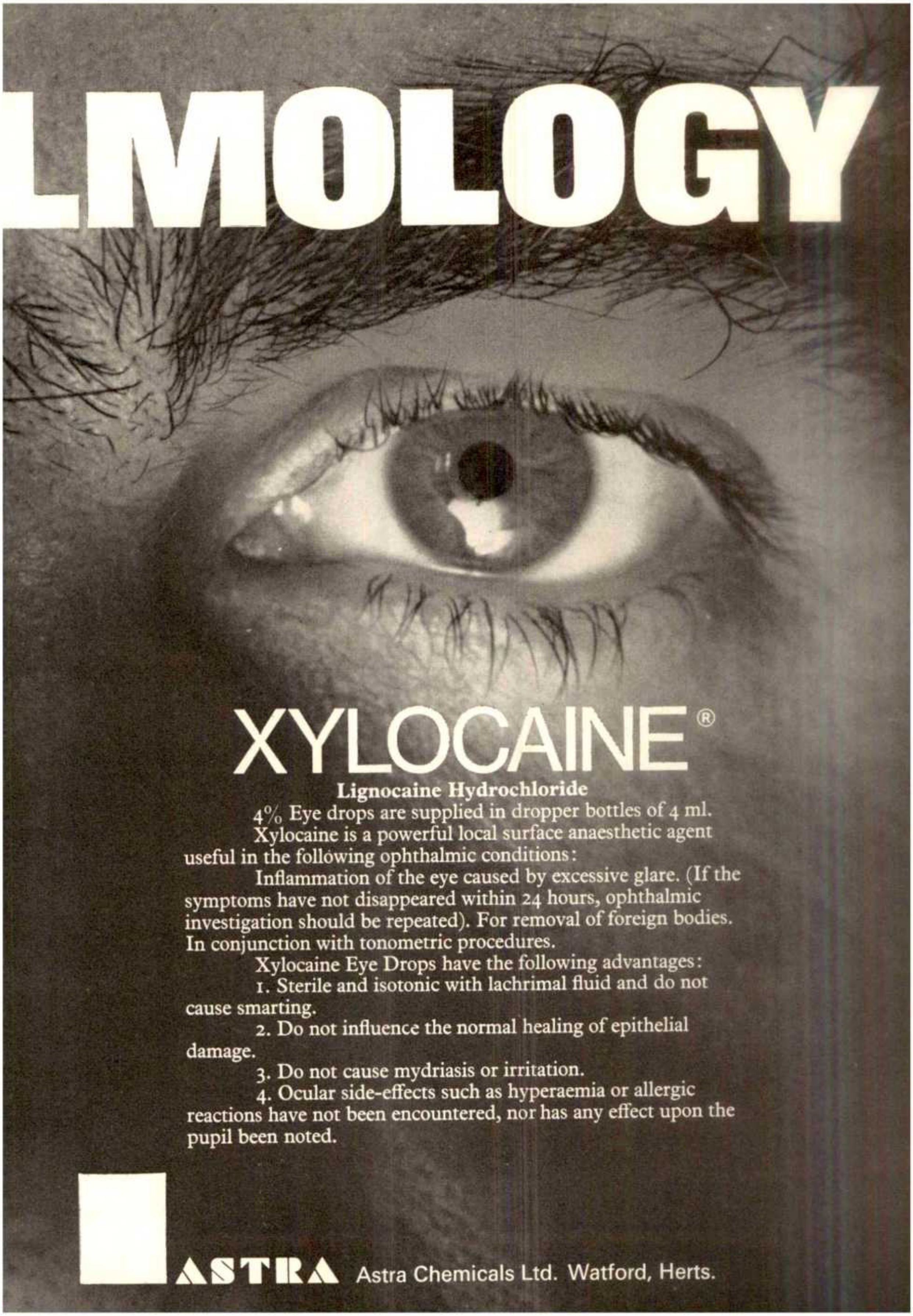

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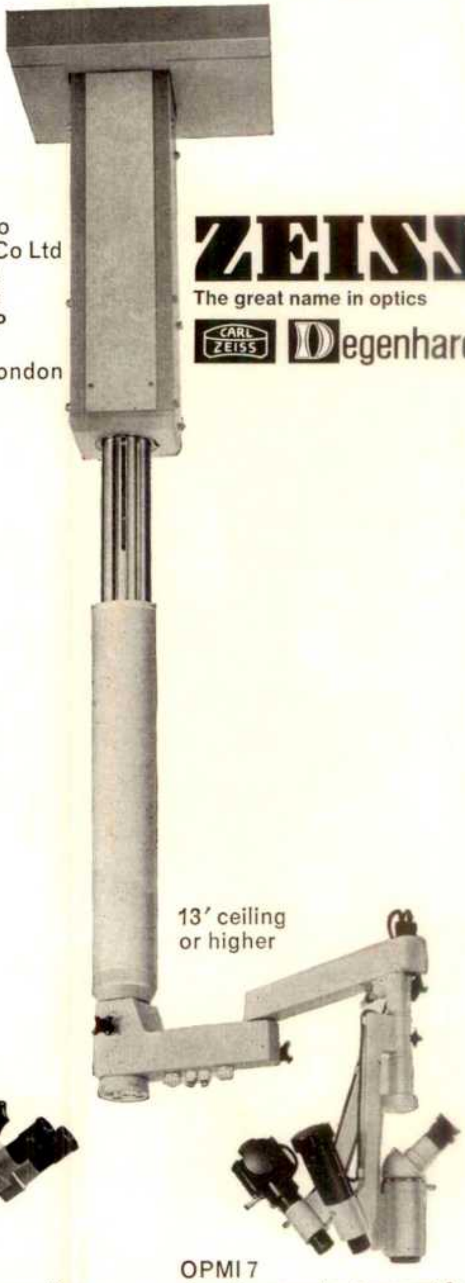

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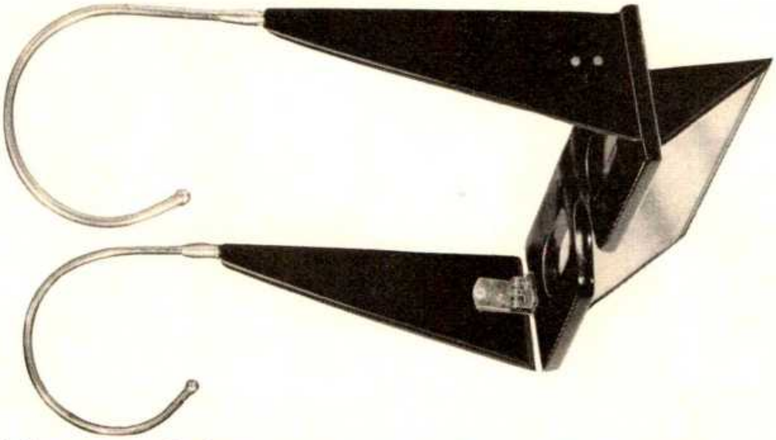

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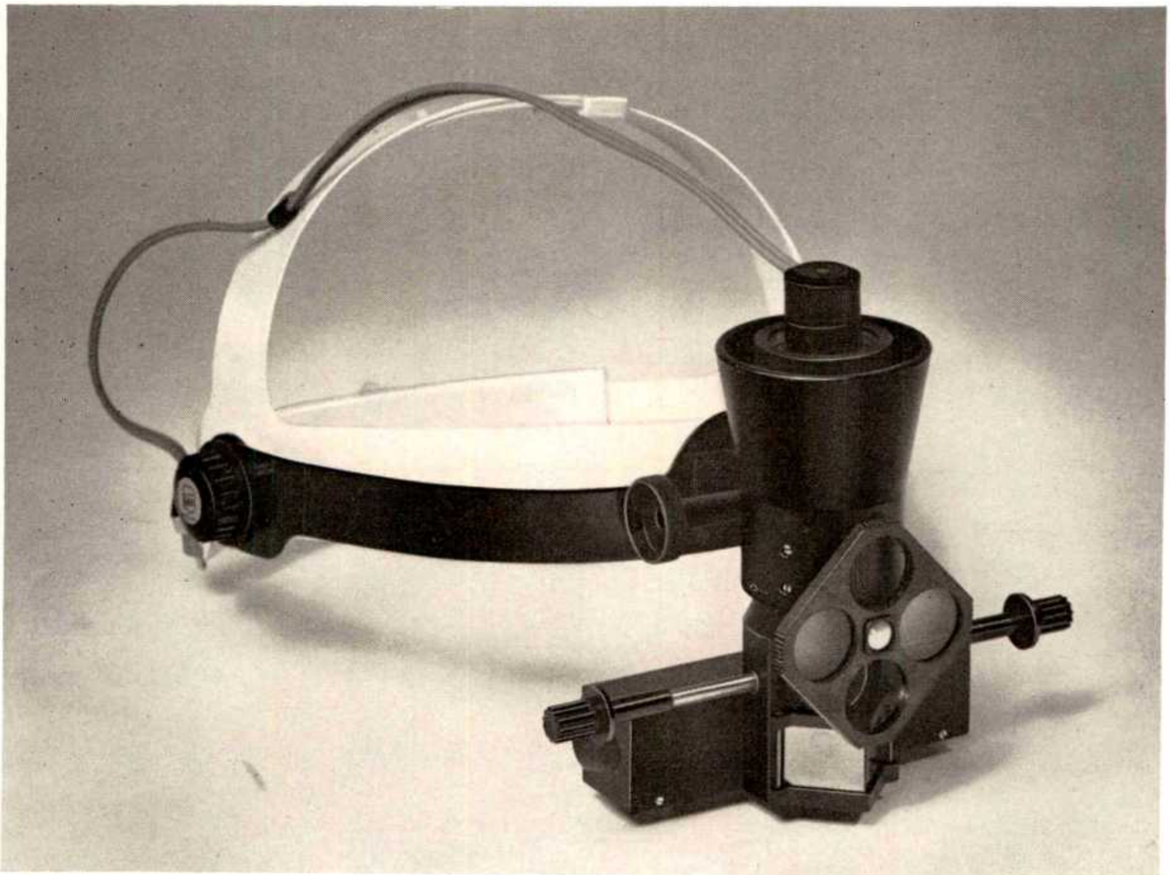

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Communications

Pituitary gland ablation by ^{90}yttrium implantation for advancing diabetic retinopathy

A further report

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The early results of treatment by ^{90}yttrium pituitary ablation in ten diabetics with advancing retinopathy were previously presented in this Journal in 1965 (Cullen, Harris, Turner, Donaldson, Munro, and Duncan, 1965a). The present report reviews the later results in these patients and in ten more recently treated diabetics.

Materials and method

All twenty subjects were selected according to the ophthalmological and, except for three, the medical criteria suggested by Field, Schepens, Sweet, and Appels (1962) and detailed by us previously (Cullen, Harris, Munro, and Duncan, 1965b). About two-thirds of all patients referred to us for treatment were rejected because the retinal changes were already too far advanced, or because of ischaemic heart disease, significant impairment of renal function, or their being considered unsuitable or otherwise unreliable in controlling their diabetes and taking the prescribed endocrine replacement therapy. Patients 1, 2, and 10 were, however, subjected to surgery despite significant renal involvement revealed by examination of biopsy material, a blood urea exceeding 60 mg./100 ml., and creatinine clearance of less than 60 ml./min.

Preoperatively all subjects were carefully assessed ophthalmologically, medically, and endocrinologically. The two ^{90}yttrium rods were placed in the pituitary fossa under television monitoring by image intensifier, the dose of radiation being calculated to deliver 100,000 r to the periphery of the gland (Cullen and others, 1965a).

Patients were reassessed 4 weeks postoperatively for evidence of reduced pituitary function, in particular:

(*a*) Decrease in severity of the diabetes as indicated by a fall in insulin requirement to 40 per cent. or less of the preoperative dose or control by diet alone in those previously requiring an oral hypoglycaemic drug.

(*b*) Reduction of the serum P.B.I. to less than 3/μg. per cent. and the thyroid 48-hour ^{131}I uptake to less than 10 per cent.

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(*c*) Absent response to the Metyrapone test, after postoperative steroid cover had been withdrawn or, if this had not been provided, a fall in plasma cortisol (11-OHCS) to a dangerously low level (Mattingly, 1962).

(*d*) Significant decrease or disappearance of the pituitary gonadotrophin levels, measured in the urine with reference to the 2nd International Reference Preparation and using the normal figures as previously defined (Loraine and Bell, 1966).

(*e*) The temporary occurrence of diabetes insipidus.

On the basis of these results patients were divided into three groups according to the estimated degree of pituitary gland destruction.

(1) COMPLETE ABLATION: These patients showed no residual pituitary function, as evidenced by criteria (*a*), (*b*), (*c*), and (*d*) above, and had developed diabetes insipidus lasting up to 40 weeks.

Table I *Preoperative data on twenty patients*

Case no.	*Age (yrs)*	*Sex*	*Duration of diabetes (yrs)*	*Hypoglycaemic therapy*	*Diabetic control*
1	50	M	11	26 i.u. lente	Good
2	54	M	14	14 i.u. Sol/22PZI	Fair
3	22	F	10	16 i.u. Sol/32 PZI	Good
4	40	F	20	16 i.u. Sol/36 PZI	Fair
5	26	F	22	32 i.u. Sol/40 PZI	Fair
6	35	F	14	20 i.u. Sol/40 PZI	Good
7	49	F	19	24 i.u. Sol/48 PZI	Fair
8	32	M	18	68 i.u. PZI	Fair
9	62	F	1	Diet only	Good
10	44	F	20	16 i.u. Sol/24 PZI	Good
11	48	F	38	16 i.u. Sol/16 PZI	Fair
12	52	M	12	125 mg. chlorpropamide	Good
13	43	M	21	16 i.u. Sol/32 PZI	Fair
14	34	M	15	32 i.u. Globin/32 PZI 20 Globin (p.m.)	Poor
15	35	M	10	24 i.u. Sol/48 PZI	Fair
16	31	M	15	20 i.u. Sol/40 PZI	Fair
17	33	F	29	24 Sol/40 PZI (a.m.) 12 i.u. Sol (p.m.)	Fair
18	51	F	15	375 mg. chlorpropamide	Good
19	30	M	26	16 i.u. Sol/60 PZI	Poor
20	28	M	14	24 i.u. Sol/20 PZI	Fair

Sol = Soluble insulin PZI = Protamine zinc insulin

(2) PARTIAL ABLATION: These patients were steroid and thyroxine dependent, but the above tests showed some residual pituitary function although this was significantly less than that determined preoperatively.

(3) UNABLATED: These patients retained virtually normal pituitary function, never having developed diabetes insipidus nor needing replacement hormonal therapy.

The patients were discharged from hospital 4 to 5 weeks after operation, taking the appropriate replacement therapy. Thereafter they were reviewed regularly at the Diabetic and Ophthalmic Clinics. One year after operation, or at a convenient time thereafter, pituitary function was re-assessed in hospital by the same tests and criteria detailed above with the exception of diabetes insipidus. Thyroxine treatment was stopped 6 weeks before admission and patients taking cortisone had the drug withdrawn under tetracosactrin cover (Synacthen, Ciba).

Table II *Preoperative renal function studies in twenty patients*

Case No.	*Blood urea (mg. per cent.)*	*Creatinine clearance (ml./min.)*	*Urinary protein (g./24 hrs)*	*Renal biopsy*
1	90	45	3·85	Advanced diffuse diabetic glomerulosclerosis Marked arteriosclerosis Patchy fibrosis – chronic pyelonephritis
2	94	54	6·00	Diffuse diabetic glomerulosclerosis Low grade chronic pyelonephritis
3	35	120	<0·03	Not performed
4	26	125	1·00	Early diffuse glomerulosclerosis
5	55	100	<0·03	Diffuse glomerulosclerosis and arteriolosclerosis Some suggestion chronic pyelonephritis
6	40	94	1·20	Advanced diffuse and nodular glomerulosclerosis
7	30	109	<0·03	Early diffuse glomerulosclerosis
8	45	120	3·40	Diffuse glomerulosclerosis and arteriolosclerosis
9	26	120	<0·03	Unsuccessful
10	65	60	1·80	Unsuccessful
11	60	60	1·30	Advanced glomerulosclerosis (diffuse and nodular)
12	46	80	0·20	Moderate diffuse glomerulosclerosis
13	32	74	0·32	Diffuse and nodular glomerulosclerosis
14	27	120	<0·03	Early diffuse glomerulosclerosis
15	34	105	0·50	Early diffuse glomerulosclerosis
16	44	80	1·20	Diffuse glomerulosclerosis
17	26	106	0·90	Early diffuse glomerulosclerosis
18	44	76	<0·03	Moderately diffuse glomerulosclerosis and arteriolosclerosis
19	32	130	0·40	Diffuse glomerulosclerosis and arteriolosclerosis
20	37	125	2·00	Diffuse and early nodular glomerulosclerosis and moderate afferent arteriolosclerosis

After reassessment the patients continued on replacement therapy, modified if necessary, and have been seen frequently as out-patients. Pituitary function was further re-evaluated at approximately yearly intervals.

An ophthalmologist (P.F.G.), who had never seen the patients before and was unaware of the degree of pituitary ablation achieved, independently assessed the ocular result by comparison of the sequential fundus photographs of each patient and, in those still living, by his own ophthalmological findings. The response to treatment was assessed on the basis of observed changes in the five following retinal components:

(1) Primary neovascularization
(2) Venous changes
(3) Vitreous haemorrhage
(4) Background retinopathy
(5) Secondary neovascularization or retinitis proliferans

The general ocular effect was considered to be:

(*a*) "Improved", if there was regression of existing and no new areas of neovascularization; no fresh vitreous haemorrhages; improvement of venous changes and background retinopathy.

(*b*) "Arrested", if neovascularization was inactivated and fibrosed and vitreous bleeding considerably reduced in frequency.

(*c*) "Unaffected", if initial neovascularization had increased unchecked and vitreous bleeding had not changed in frequency or had increased.

Results

Table I (see p. 218) shows the individual data of the twenty patients.

Table II (see p. 219) records the preoperative renal function in the treated patients.

Table III (opposite) gives the category of pituitary ablation at 4 weeks postoperatively, at 1 year after operation, and at the most recent review, along with the summarized ocular results.

Table IV (overleaf, p. 224) sets out the endocrine criteria used to categorize the degree of ablation achieved.

Table V (overleaf, pp. 222–223) details the results with regard to the five retinal components studied when possible in each patient.

Seven patients have died, two from postoperative meningitis, one from severe hypoglycaemia, and four from renal or cardiovascular disease (Table III).

Twelve patients were considered to be completely ablated postoperatively. Eight (Nos 1, 3, 4, 13, 15, 17, 19, and 20) have subsequently shown no sign of returning pituitary function and have benefited from the operation, the retinopathy either being arrested or showing improvement. Of the remaining four patients, three (Nos 5, 10, and 11) have shown signs of returning pituitary function and in two (Nos 10 and 11) this was associated with some reactivation and increase in the retinopathy. The fourth patient (No. 14) died before adequate follow-up was obtained, but his retinopathy appeared to have been arrested.

Seven patients were found to be only partially ablated at the initial postoperative assessment; of these one patient (No. 2) died of meningitis, and one (No. 8) showed a steady return of pituitary function to normal. His retinopathy, which postoperatively appeared to be quiescent, became active before he died. He is the only patient in whom pituitary function continued to return after a one-year assessment. The remaining five have

Table III *Results of treatment in twenty patients*

Case no.	*Category of ablation*			*Ocular result when last seen*	*Date of operation*	*Remarks*
	Postoperative	*At 1 year*	*When last seen*			
1	Complete	Complete	Complete	Arrested	Dec., 1963	Died 29 months after operation (Renal failure)
2	Partial	–	–	–	Jan., 1964	Died 4 weeks after operation (Meningitis)
3	Complete	Complete	Complete	Improved	Dec., 1963	
4	Complete	Complete	Complete	Arrested	Feb., 1964	
5	Complete	Partial	Partial	Improved	Mar., 1964	Adrenal function returned at 1 year
6	Partial	Partial	Partial	Arrested	Mar., 1964	Always residual pituitary function
7	Partial	Partial	Partial	Unaffected	Apr., 1964	
8	Partial	Partial	Unablated	Arrested	Oct., 1964	See text. Died 50 months after operation (Myocardial infarct)
9	Partial	Partial	Partial	Unaffected	Nov., 1964	Died 46 months after operation (Cerebral thrombosis)
10	Complete	Partial	Partial	Arrested	Nov., 1964	Died 45 months after operation (Renal failure)
11	Complete	Partial	Partial	Unaffected	Mar., 1965	Pituitary function returning at 1 year
12	Partial	Partial	Partial	Arrested	June, 1965	See text
13	Complete	Complete	Complete	Improved	Jan., 1966	
14	Complete	–	–	–	Jan., 1966	Died 7 months after operation (Recurrent meningitis)
15	Complete	Complete	Complete	Improved	Feb., 1966	Died 25 months after operation (Hypoglycaemia)
16	Partial	Partial	Partial	Arrested	May, 1966	Residual but static pituitary function
17	Complete	Complete	Complete	Arrested	June, 1966	
18	Unablated	Unablated	Unablated	Unaffected	July, 1966	See text
19	Complete	Complete	Complete	Arrested	Nov., 1966	
20	Complete	Complete	Complete	Arrested	Apr., 1967	

apparently had a static impairment of pituitary function. In three (Nos 6, 12, and 16) the retinopathy has remained quiescent and arrested, but in the other two (Nos 7 and 9) the retinopathy became much worse. No patient in this group showed improvement in the retinopathy.

One patient (No. 18) who was insulin independent showed no decrease in pituitary function after operation. She had a rapidly progressing retinopathy with further severe haemorrhage shortly after the procedure and was not considered suitable for further surgical treatment.

Cerebrospinal fluid rhinorrhoea is still a major postoperative complication and occurred in three cases of this series. Two patients were observed to have transient palsies of the extraocular muscles for 4 to 6 weeks following insertion of ^{90}yttrium.

Discussion

There is still no agreement on the most effective method of performing a pituitary ablation and on whether complete destruction of the gland is necessary to achieve the maximum therapeutic benefit in patients with diabetic retinopathy. It has been reported that pituitary irradiation causing suppression and not ablation of the gland will produce acceptable ocular results (Linfoot, 1967). In most series, however, the impression has

Table V *Results for the five retinal components studied*

Time of examination	*Retinal component*	*Neovascularization*		*Vitreous haemorrhage*	
	Eye	*Right*	*Left*	*Right*	*Left*
Postoperative result	None	7	1	7 14 15 19 20	1 2 6 7 13 8
	Early		2 19		
	Moderate	6 8 13 15	6 12 13 15	6 8 13 17	17 19 20
	Marked	1 2 3 4 5 9 10 11 12 14 16 17 18 19 20	3 4 5 7 8 9 10 11 14 16 17 18 20	1 2 3 4 5 9 10 11 12 16 18	3 4 5 8 9 1 11 12 15 16
Latest post-operative result	Regressed	5 13 15	5 13		
	Arrested	1 3 4 6 10 16 17 19 20	3 4 6 8 12 15 16 17 19 20	1 3 4 5 6 7 8 10 13 15 16 17 19 20	1 3 4 5 6 8 12 13 15 16 17 20
	Unchanged	8		11	11
	Progressed	7 9 11 12 18	1 7 9 10 11 18	9 18	7 9 18 19

Figures refer to case numbers Missing numbers indicate no follow-up or component not visualized

been that the best results occur only if the pituitary gland is totally destroyed (Luft, Olivecrona, and Sjogren, 1955; Joplin, Fraser, Hill, Oakley, Scott, and Doyle, 1965; Bradley, Rees, and Fager, 1965; Rucker, Gastineau, and Svien, 1967; Field, 1967). One controlled study, which evaluated the effect of three different doses of ^{90}yttrium radioactivity, demonstrated that "maximal" and "intermediate" ablation appeared equivalent in effect but clearly superior to "slight" ablation. Venous irregularities improved discernibly only after maximal ablation (Joplin, Oakley, Hill, Kohner, and Fraser, 1967), and this is of particular importance as these lesions are not amenable to photocoagulation. The present results support the view that complete ablation is required to achieve maximal ocular benefit. All those having complete ablation showed either improvement or arrest of retinopathy, whereas only half of those having partial ablation showed a similar response. They also confirm the importance of careful medical preoperative assessment, in that the three patients who did not fulfil the previously defined criteria for selection have died. The poor prognosis for vision and survival in this type of patient has recently been emphasized (Deckert, Simonsen, and Poulsen, 1967; Teuscher, Escher, König, and Zahnd, 1970).

Neovascularization, which is the most serious manifestation of diabetic retinopathy, was improved or arrested in 22 eyes of thirteen patients. Neovascularization arising from the optic disc, which was present to a varying degree in all patients of our series, appears to be effectively treated only by means of a pituitary ablation. More peripheral and localized areas of new vessel formation can, however, be effectively eradicated by photo- or laser-coagulation. In two of the patients reported (Nos 3 and 19), photocoagulation therapy was carried out 5 and 2 years respectively after pituitary operation, because of incomplete regression of peripheral neovascularization which was still considered to be a potential source of vitreous haemorrhage.

ackground retinopathy		*Venous change*		*Retinitis proliferans*	
ight	*Left*	*Right*	*Left*	*Right*	*Left*
				7 8 14 15 17 19	1 2 5 6 14 16 17 19
				5 6 20	11 13 18 20
8 13 19	3 6 7 12 13 19	4 7 8 10 13 19	1 4 6 7 12 13 19	3 10 13 18	3 12
2 3 4 5 6 9 10 1 14 15 16 17 8 20	1 2 4 5 9 11 14 15 16 17 18 20	1 2 3 5 6 9 11 14 15 16 17 18 20	2 3 5 9 11 14 15 16 17 18 20	1 2 4 9 11 12 16	4 7 8 9 10 15
5 17	15	1 3 5 15 17 20	1 3 15		
3 4 5 6 8 10 1 13 16 19 20	3 4 5 6 12 13 16 17 18 20	4 8 13 16 19	4 5 12 13 16 17 18 20	3 13 15	3 13 16
	1 9 11 19	6 9 10 11	6 9 11 19		
18	7	7 18	7	1 4 5 6 7 8 9 10 11 12 16 17 18 19 20	1 4 5 6 7 8 9 10 11 12 15 17 18 19 20

Cryohypophysectomy as an alternative method of destroying the pituitary gland has been advocated (Rand and Roth, 1967). We have used this method in only three diabetic patients during our early experience of this technique and, in these, adequate destruction of the gland was not achieved. We have not, therefore, used this method again in other diabetic patients.

In conclusion, we believe that pituitary ablation, though a serious and potentially dangerous undertaking, can in properly selected patients effectively arrest various forms of advancing diabetic retinopathy which cannot be treated by photo-coagulation and would otherwise eventually lead to blindness.

Summary

The results of pituitary gland ablation in twenty diabetic patients with proliferative retinopathy are given with reference to endocrinological and ophthalmological data. The average follow-up period was 5 years. When the category of pituitary ablation achieved is related to the ocular results, it is concluded that a complete destruction of the gland should be the goal of treatment.

We are indebted to the W. H. Ross Foundation (Scotland) for the Prevention of Blindness for a generous donation towards the the cost of the television monitoring equipment used in the operation.

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Table IV *Category of ablation with criteria employed in twenty patients*

Case No.	*Category of ablation postoperatively*	*Criteria**	*Category of ablation at 1 year*	*Criteria**	*Category of ablation when last seen*
1	Complete	abcde	Complete	abcd	Complete
2	Partial	ab	–	–	–
3	Complete	abcde	Complete	abcd	Complete
4	Complete	abcde	Complete	abcd	Complete
5	Complete	abcde	Partial	ab d	Partial
6	Partial	ab	Partial	ab	Partial
7	Partial	ab d	Partial	ab d	Partial
8	Partial	a c	Partial	–	Unablated
9	Partial	bc	Partial	bc	Partial
10	Complete	abcde	Partial	b d	Partial
11	Complete	abcde	Partial	bcd	Partial
12	Partial	bcd	Partial	bcd	Partial
13	Complete	abcde	Complete	abcd	Complete
14	Complete	abcde	–	–	–
15	Complete	abcde	Complete	abcd	Complete
16	Partial	abc	Partial	abc	Partial
17	Complete	abcde	Complete	abcd	Complete
18	Unablated	–	Unablated	–	Unablated
19	Complete	abcde	Complete	abcd	Complete
20	Complete	abcde	Complete	abcd	Complete

N.B. *Letters under "Criteria" refer to the tests, detailed in the text, which showed complete ablation. (Thus complete ablation = abcde.)

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Diabetic retinopathy and hypertension

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Both hypertension and diabetes cause retinopathy. The two conditions produce similar retinal lesions, but their pattern differs so that it is often easy to distinguish between hypertensive and diabetic retinopathy with the ophthalmoscope. It might be expected, therefore, that, in patients with diabetes and hypertension, a different pattern of retinal lesions would be found from that seen in patients with diabetes alone. Very little has been written concerning this, and most observations have depended on ophthalmoscopic assessment of the retina. In the present study the retinal photographs of 63 diabetics with retinopathy, some hypertensive and some normotensive, were compared.

Material

The 63 patients studied (27 men and 36 women) had all been selected from the diabetic clinics of the Bristol Royal Infirmary to take part in a trial of clofibrate as treatment for their diabetic retinopathy (Harrold, Marmion, and Gough, 1969). Selection was somewhat biased in favour of those patients showing the most advanced hard retinal exudation but, provided a clear view of the retina could be obtained in at least one eye, no other criteria were used in selection. None had papilloedema or were receiving hypotensive drugs, and none were nephrotic or had advanced renal failure.

The age distribution is shown in Table I. Five were newly discovered diabetics, and the remainder had had diabetes for at least one year.

Table I *Age and blood pressure*

Age group (yrs)	*No. of patients*	*Percentage of total*	*Diastolic blood pressure (mm.Hg)*	
			90 *or less*	*More than* 90
20–29	0	–	0	0
30–39	8	13	7	1
40–49	9	14	6	3
50–59	21	33	10	11
60–69	21	33	9	12
70–79	4	7	0	4
Total	63	100	32	31

Methods

Retinal photographs were taken using a Zeiss retinal camera and Kodachrome II daylight film. Nine exposures were made of each eye to include the optic disc and eight adjacent fields showing the four main vessels and their intervening regions. These photographs were graded by the method of Oakley, Hill, Joplin, Kohner, and Fraser (1967), which involves the comparison of each retinal photograph with standard photographs illustrating severity of retinal involvement by haemorrhages and microaneurysms, by hard exudates, by new vessel formation, by retinitis proliferans, and by venous disease. Assessment of haemorrhages and microaneurysms depended upon their numbers, but hard exudation, new vessel formation, and retinitis proliferans depended upon the area of retina involved. A numerical grading of 0 to 5 was made for each of these lesions, and by dividing

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the number of photographs examined for each eye into the sum of the gradings for these photographs a mean grading for each type of lesion was calculated for each eye. These mean gradings were used as a basis for the study of the relationship between retinal appearance and blood pressure.

Soft retinal exudation was recorded and graded numerically by counting the number of poorly-defined white retinal patches on each photograph; a mean grading was calculated as for the other lesions. In addition to the above assessment, the photographs were all reviewed and a record made of the incidence of preretinal haemorrhages, linear or nerve fibre layer haemorrhages, and macular star formation. A macular star was defined as any area of hard exudation arranged in radial streaks around the fovea; it was considered to be present even if there was only one such streak.

The blood pressure was recorded in the out-patient department with a standard mercury sphygmomanometer on at least two occasions in each patient. A diastolic blood pressure of 90 mm.Hg was chosen as the point at which the patients were separated into hypertensive and normotensive groups. There were 31 patients in the former group and 30 in the latter. Some further comparisons were made between ten patients with diastolic pressures of 110 mm.Hg or more and those in the normotensive group.

The patients were further divided into those with evidence of arteriosclerosis and those without. The former group had either angina pectoris or previous myocardial infarction or an abnormal electrocardiogram suggesting ischaemic heart disease, or they had evidence of peripheral vascular disease in the legs.

The statistical significance of differences was calculated using the χ^2 test unless stated otherwise (Yates' correction for small numbers was used whenever the number of eyes in any subgroup was less than 10).

Results

I. INTRAOCULAR HAEMORRHAGE AND SYSTEMIC BLOOD PRESSURE

(*A*) *Retinal haemorrhages*

Table II shows that there was no significant difference in the grading for retinal haemorrhages in the high and low blood pressure groups, 84 per cent. of eyes from patients with a diastolic blood pressure above 90 mm.Hg having the more severe grading for retinal haemorrhages compared with 75 per cent. in the normotensive group. On the other hand, when linear retinal haemorrhages were considered alone, there was an incidence of 57 per cent. in eyes from hypertensives and 37 per cent. in eyes from normotensives. In eyes from patients with diastolic blood pressures in excess of 110 mm.Hg, the incidence of linear haemorrhages was 78 per cent. (Table III).

(*B*) *Preretinal haemorrhages*

These were present in 20 per cent. of eyes from the hypertensive group and in 10 per cent. of those from the normotensive group. The total number of eyes involved by preretinal haemorrhage was small and the differences could not be shown to be significant even when eyes from patients with a diastolic blood pressure of 110 mm.Hg or more were compared with the normotensive group (Table IV).

Of the eighteen eyes with preretinal haemorrhages, three could not be assessed for retinal changes; in the remainder eleven had proliferative lesions and ten had linear haemorrhages, either one or other of these lesions being present in each eye. In ten eyes from the hypertensive group with preretinal haemorrhages, nine had linear haemorrhages, whereas the incidence of linear haemorrhages was only 50 per cent. in the rest of the hypertensive group. This difference was significant at the 2 per cent. level (Table V). In the normotensive group with preretinal haemorrhages there was only one eye with linear haemorrhages; the others all had proliferative changes. As expected there was a positive correlation between preretinal haemorrhages and proliferative changes (Table V).

Table II *Relationship between blood pressure and gradings for various retinal lesions*

		Diastolic blood pressure (mm.Hg)				
		More than 90		*90 or less*		
Retinal lesion	*Grading*	*No. of eyes*	*Percentage in each group*	*No. of eyes*	*Percentage in each group*	*Probability* χ^2
Haemorrhage	0–0·99	9	16	15	25	χ^2 = 1·103 P = <0·3 >0·2
	1+	47	84	44	75	
	Total	56	100	59	100	
Hard exudates	0	3	5	8	14	
	0·99 or less	31	55	24	41	
	1+	22	40	27	45	
	Total	56	100	59	100	
New blood vessels	0	40	71	45	76	
	0·99 or less	14	25	12	20	
	1+	2	4	2	4	
	Total	56	100	59	100	
Retinitis proliferans	0	50	89	54	91	
	1·99 or less	6	11	0	–	
	2+	0	–	5	9	
	Total	56	100	59	100	
Venous disease	0–2·99	21	38	32	55	χ^2 = 3·528 P = <0·1 >0·05
	3+	35	62	26	45	
	Total	56	100	58*	100	
Soft exudates	0	28	50	29	49	χ^2 = 3·595 P = <0·20 >0·10
	0·99 or less	20	36	23	39	
	1+	8	14	7	12	
	Total	56	100	59	100	

* One eye could not be assessed

II. RETINAL EXUDATION AND SYSTEMIC BLOOD PRESSURE

(*A*) *Hard exudates*

Table II shows that 39 per cent. of eyes from patients in the hypertensive group had the more severe gradings for hard exudation compared with 46 per cent. in the normotensive group; the difference was not significant, neither was there a significant difference between eyes from patients with a diastolic blood pressure of 110 mm. Hg or more and those from the normotensive group (Table VI); both comparisons seemed to favour the hypertensive eyes as having less exudation, but the normotensive group had more eyes free from exudates.

Table III *Linear haemorrhages and blood pressure*

Linear haemorrhage	*Diastolic blood pressure (mm.Hg)*					
	More than 90		90 *or less*		110 *or more*	
	No. of eyes	*Percentage in each group*	*No. of eyes*	*Percentage in each group*	*No. of eyes*	*Percentage in each group*
Present	32	57	22	37	14	78
Absent	24	43	37	63	4	22
Probability			$\chi = 4{\cdot}528$ $P = <0{\cdot}05$		$\chi = 7{\cdot}593$ $P = <0{\cdot}01$	

Table IV *Preretinal haemorrhages and blood pressure*

Preretinal haemorrhage	*Diastolic blood pressure (mm.Hg)*					
	More than 90		90 *or less*		110 *or more*	
	No. of eyes	*Percentage in each group*	*No. of eyes*	*Percentage in each group*	*No. of eyes*	*Percentage in each group*
Present	12	20	6	10	5	26
Absent	47	80	54	90	14	74
Probability			$\chi = 1{\cdot}770$ $P = <0{\cdot}20$		$\chi = 1{\cdot}980$ $P = <0{\cdot}20$	

There were four eyes in which preretinal haemorrhages were seen but which could not be assessed for retinal changes. The inclusion of these eyes in this Table accounts for the increased totals

Table V *Preretinal haemorrhages in the eyes of patients with diastolic blood pressure of more than* 90 *mm.Hg and their relationship with linear haemorrhages and proliferative retinopathy*

Lesions		*Preretinal haemorrhage (No. of eyes)*		*Probability*
		Present	*Absent*	
Linear haemorrhage	Present	9	23	Fisher's exact significance P = 0·0215
	Absent	1	23	
	Total	10	46	
Proliferative retinopathy	Present	7	10	$\chi^2 = 6{\cdot}087$ $P = <0{\cdot}02$
	Absent	3	36	
	Total	10	46	

Macular star formation, as defined above, was present in 25 per cent. of eyes from patients in the hypertensive group and in 20 per cent. of eyes from the normotensive group (Table VII). The incidence in patients with a diastolic blood pressure of 110 mm.Hg or more was 22 per cent. (four out of eighteen). There was therefore no evidence of an association between hypertension and macular star formation.

Table VI *Hard retinal exudation and blood pressure*

Hard exudation	*Diastolic blood pressure (mm.Hg) (No. of eyes)*	
	110 or more	*90 or less*
Absent	0	8
Graded less than 0·99	13	24
Graded 1 or more	5	27
Total	18	59

Table VII *Macular star formation and blood pressure*

Macular star	*Diastolic blood pressure (mm.Hg)*					
	More than 90		*90 or less*		*110 or more*	
	No. of eyes	*Percentage in each group*	*No. of eyes*	*Percentage in each group*	*No. of eyes*	*Percentage in each group*
Present	14	25	12	20	4	22
Absent	42	75	47	80	14	78
Total	56	100	59	100	18	100

(*B*) *Soft exudates*

These were present in 50 per cent. of eyes from the hypertensive group and in 51 per cent. from the normotensive group (Table II). Table VIII shows the incidence in eyes of patients with a diastolic blood pressure of 110 mm.Hg or more to be 61 per cent. compared to 51 per cent. in the normotensive group; these differences were not significant.

Table VIII *Soft retinal exudates and blood pressure*

Soft exudates	*Diastolic blood pressure (mm.Hg)*			
	110 or more		*90 or less*	
	No. of eyes	*Percentage in each group*	*No. of eyes*	*Percentage in each group*
Absent	7	39	29	49
Graded less than 0·99	7	39	23	39
Graded 1 or more	4	22	7	12
Totals	18	100	59	100

III. VENOUS DISEASE AND SYSTEMIC BLOOD PRESSURE

A grading of more than 3 for venous abnormalities was found in 62 per cent. of eyes from the hypertensive group and in 45 per cent. from the normotensive group. These differences were not significant at the 5 per cent. level (Table II). The incidence of this grading in eyes from patients with a diastolic blood pressure of 110 mm.Hg or more was 44 per cent. These figures favour a correlation between severe venous disease and hypertension.

IV. RETINITIS PROLIFERANS

This type of lesion was present in six eyes from the hypertensive group and five from the normotensive group, the latter showing more extensive retinal involvement.

V. NEW BLOOD VESSELS

These were seen in sixteen eyes from patients in the hypertensive group and in fourteen from the normotensive group. The extent of involvement was similar in the two groups.

VI. ARTERIOSCLEROSIS AND RETINOPATHY

Table IX shows the severity of retinal lesions in patients with evidence of ischaemic heart disease or peripheral vascular disease compared with those in patients free from evidence of such lesions. There are no statistical differences between the two groups.

Table IX *Arteriosclerosis and retinopathy*

Retinal lesion	*Grade*	*Arteriosclerosis*			
		Evidence (52)		*No evidence* (63)	
		No. of eyes	*Percentage in each group*	*No. of eyes*	*Percentage in each group*
Haemorrhage	0–1·99	11	21	13	21
	2+	41	79	50	79
Hard exudate	0	3	6	8	13
	<0·99	25	48	30	48
	1+	24	46	25	39
New blood vessels	0	36	69	49	78
	<0·99	13	25	13	21
	1+	3	6	1	2
Retinitis proliferans	0	45	87	59	94
	<1·99	4	8	2	3
	2+	3	6	2	3
Venous disease	*0–2·99	23	44	*30	48
	3+	29	56	32	52
Soft exudates	0	23	44	34	54
	<0·99	23	44	20	32
	1+	6	12	9	14

* One eye could not be assessed for venous disease

Discussion

Mackenzie and Nettleship (1879) were the first to make detailed descriptions of retinopathy in diabetes. Over the following 50 years it was disputed whether or not diabetic retinal disease was distinct from hypertensive retinal disease. Papers by Gray (1933) and Wagener, Dry, and Wilder (1934) established that retinopathy occurred in diabetics in the absence of hypertension or albuminuria. Since this discovery little has been written about the relationship between hypertension, diabetes, and retinopathy. Larsen

(1960), in an extensive study of diabetics with a review of the literature, stated that "cotton wool exudates or macular star formation are not characteristic diabetic lesions in the retina but they may be seen when diabetes is complicated by nephropathy or hypertension". Esmann, Lundbaek, and Madsen (1963), in a study of 211 diabetics with retinopathy, found after careful ophthalmoscopic assessment that hard exudates were more common in patients with diastolic blood pressures between 100 and 110 mm.Hg than in those with lower pressures ($P = < 0{\cdot}01$) but that the incidence of soft exudates was unaffected by blood pressure. Kohner, Fraser, Joplin, and Oakley (1969), studying the effects of diabetic control on retinopathy in 104 patients, found that retinal haemorrhages and new blood vessel formation could not be correlated with blood pressure. These conclusions resulted from the assessment of retinal photographs by the method of Oakley and others (1967).

The present study, using the same method of assessment, confirmed these findings concerning retinal haemorrhages and new vessel formation. However, when linear or flame-shaped haemorrhages were assessed alone, there was a clear correlation between raised diastolic blood pressure and their presence ($P = < 0{\cdot}01$). These linear haemorrhages were not confined to eyes from hypertensive patients, but were also present in 37 per cent. of the eyes from the normotensive group.

Preretinal haemorrhages are a common accompaniment of the early stages of proliferative retinopathy (King, Dobree, Kok, Foulds, and Dangerfield, 1963), but these haemorrhages often appear in areas of the retina not involved by new blood vessels, though a track of blood may be found leading from new vessels to a preretinal collection of blood (Taylor, 1969), or the haemorrhages may appear in eyes in which no new vessels can be seen. In the present survey a correlation was observed between proliferative retinopathy and preretinal haemorrhages, but there was also a correlation between linear haemorrhages and preretinal haemorrhages. There were three eyes in which no proliferative changes were seen, but all had linear haemorrhages. These linear haemorrhages lie near the anterior border of the retina and therefore occur in a position that could allow the preretinal escape of blood.

One interpretation of these findings is that the correlation of the incidence of linear haemorrhages with preretinal haemorrhages and raised blood pressure respectively suggests that, in diabetics with hypertension and linear haemorrhages, control of blood pressure may prevent at least a few of the preretinal haemorrhages that occur. It could also be said that the absence of new vessels on retinal colour photographs does not necessarily mean that none are present and that all preretinal haemorrhages arise from bleeding new vessel systems. No study is available to show whether or not preretinal haemorrhage occurs in the absence of new vessels as shown on fluorescein photography.

Hard and soft retinal exudates had a similar severity and incidence in the eyes of both hypertensive and normotensive patients. Macular star formation, as defined above, also had a similar incidence in the eyes of the two groups of patients. The definition of macular star formation used has included many eyes that would not otherwise have been considered to show this phenomenon. Yanoff (1969) has shown that hard retinal exudates in the macular region may occur in the nerve fibre layer of the retina and may thus become arranged in a star around the fovea. Most hard exudates occur in the outer plexiform layer (Bloodworth, 1962). The arrangement of the exudation therefore gives some indication of the site of retinal involvement. For this reason it was thought justifiable to include single radially arranged streaks of hard exudation in the macular region as macular star formation.

Kohner, Dollery, and Bulpitt (1969) have shown that soft exudates in diabetic retinopathy are nearly always associated with arteriolar abnormality in the region of exudation, indicating that disease of the smaller arteries may be of importance in diabetic retinopathy. The patients in the present study were grouped into those with evidence of ischaemic heart disease or peripheral vascular disease or both, and those without such lesions. A comparison of the retinal appearance in the two groups showed no significant differences; in particular the incidence of soft exudates was 54 per cent. in the arteriosclerotic group and 46 per cent. in the others, a difference which is not significant.

From this survey it seems that systemic blood pressure makes little difference to the appearance of the retina in diabetics with retinopathy, beyond altering the incidence of linear haemorrhages. When each of six lesions of the retinal disease was compared in the two blood pressure groups, no significant differences were shown (Table II), though in each case either the incidence or the severity of the lesion concerned was greater in the hypertensive group. The site of retinal bleeding was significantly more frequent in the nerve fibre layer in the hypertensive group.

It should be emphasized that these findings are relevant only to the group of patients studied, that 73 per cent. of all the patients were over 50 years old, and that only four patients in the hypertensive group were less than 50 years (Table I).

Summary

A detailed study of the retinal photographs of 63 patients selected to take part in a controlled trial of clofibrate as treatment for their diabetic retinopathy demonstrated little or no difference in the initial appearance of the retina in those with hypertension compared with the retina in those without hypertension. The only correlation found was that between linear or nerve fibre layer haemorrhages and hypertension. The correlation between these haemorrhages and preretinal haemorrhages is discussed.

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Traumatic optic pathway degeneration

Antegrade and retrograde

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In the case to be presented degeneration of the optic pathway occurred in both antegrade and retrograde fashion after injury to both optic nerves. In the left eye and possibly in the right as well, not only did the ganglion-cell layer degenerate, but the in nernuclear layer of the retina was also involved. This exemplified retrograde trans-synaptic degeneration.

Case report

A 33-year-old white man was shot in the head in December, 1955, with a ·22 calibre bullet. He denied loss of consciousness, but stated that he felt "as if the lights had gone out". A wound of entry was present 2–2½ cm. posterior to and on a level with the external bony angle of the left orbit. His peripheral neurological examination was essentially negative. He noted a mild numb sensation about the left eye. There was a subconjunctival haemorrhage of the left eye. Horizontal ocular movements of the left eye were absent. Only slight superior rectus action remained. There was ptosis of the left upper eyelid. On the left side corneal sensation was reduced and sensation to pinprick was moderately decreased over the ophthalmic branch of the trigeminal nerve. There was slight fuzziness of the edges of the left optic disc; the veins inferiorly were full; no retinal haemorrhages or papilloedema were seen. Both pupils were dilated and did not react to light. There was no light perception in either eye.

In the right eye ocular motility was intact and the retina and optic nerve head appeared normal. Skull *x* rays showed a tract through the posterior orbital cavity on the left and a missile just past the midline to the right side at the level of the ethmoid, just above the medial portion of the superior orbital fissure.

On the day of admission the orbits were unroofed surgically, and haemorrhages and oedema of the periorbital tissues were found on the left. The left optic nerve was intact, but the neurosurgeon did not elevate or rotate the nerve to see if its inferior surface was damaged. He felt that the bullet had passed beneath the left optic nerve. The bullet was found on the right side adjacent to the medial wall of the right optic canal.

In June, 1956, it was reported that the patient had no light perception, no pupillary reaction, and total bilateral optic atrophy.

The patient died at the age of 45 in November, 1968, nearly 13 years after being shot, having been found unconscious in his apartment.

PERTINENT AUTOPSY FINDINGS

Adhesions were present on the under surface of the brain in the region of the optic chiasm. The olfactory nerves and the optic nerves, chiasm, and tracts were intact, but atrophic and flattened. The proximal portions of the remaining cranial nerves were grossly unremarkable. The base of both frontal lobes showed evidence of old contusion. Both orbital plates were absent. The anterior

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clinoid processes and posterior aspect of the cribriform plate were shattered and fibrous tissue was adherent to them.

The remainder of the autopsy showed no unusual findings. Toxicological analysis of the liver revealed barbiturates in the amount of 16·5 mg./100 g., and death was attributed to acute barbiturate poisoning.

Gross examination of eyes

The left eye measured 25 × 24 × 24 mm. The cornea was clear and the anterior chamber depth normal. There was a small freckle on the iris near the pupillary border at 3.30 o'clock.

The eye was opened horizontally. There was an oval macular hole and a pigmented chorioretinal scar below the macula.

The right eye measured 25 × 25 × 24·5 mm. The cornea was clear and the anterior chamber unremarkable. The eye was opened vertically. The lens, retina, and vitreous were in place. The optic nerve head was unremarkable.

Microscopical examination

LEFT EYE:

In some sections a chorioretinal scar was seen at the posterior pole (Fig. 1), while in other sections there was a zone of severe retinal thinning involving all but the outer nuclear layer (Fig. 2). In this zone the inner limiting membrane was somewhat wrinkled. Still other sections showed the macular hole (Fig. 3). In all sections the ganglion-cell and nerve-fibre layers were markedly atrophic and there was thinning of the inner nuclear layer (Fig. 4). A few inconspicuous cystic spaces were present in the inner nuclear layer.

RIGHT EYE:

There were scattered small lymphocytes in the iris. Many small vacuoles were present in the superficial lens cortex. The ganglion-cell and nerve-fibre layers of the retina were markedly atrophic

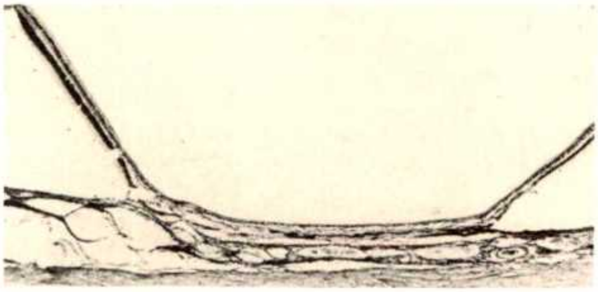

FIG. 1 *Chorioretinal scar below macula of left eye. Haematoxylin and eosin.* ×23

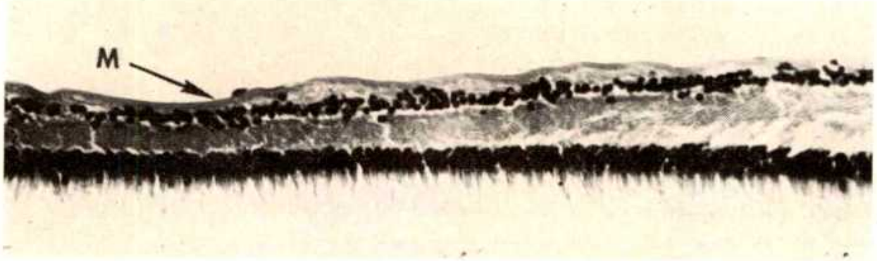

FIG. 2 *Retina near posterior pole of left eye, showing loss of nerve-fibre and ganglion-cell layers and severe thinning of inner nuclear layer. Inner limiting membrane (M) is wrinkled. Haematoxylin and eosin.* ×224

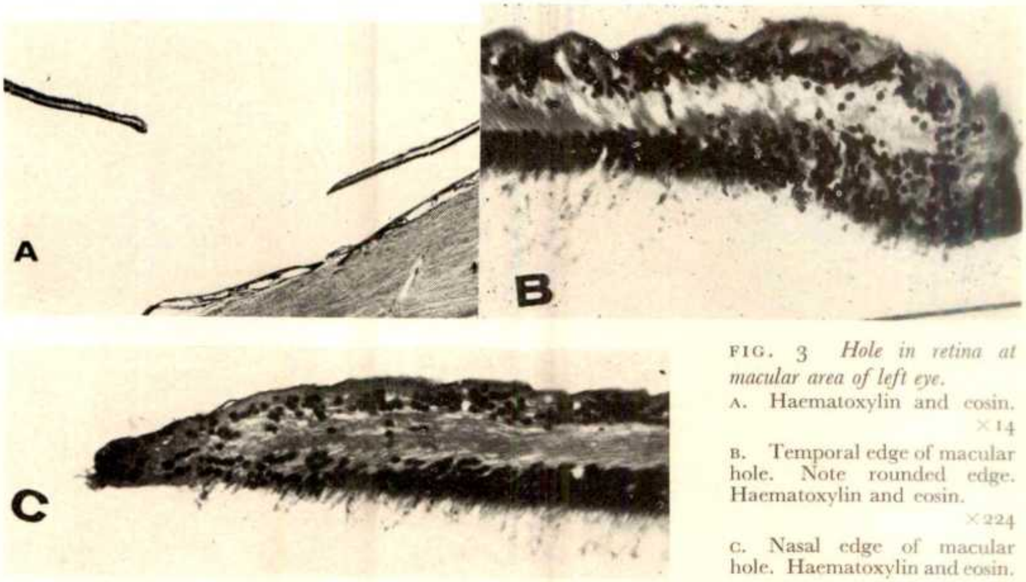

FIG. 3 *Hole in retina at macular area of left eye.*
A. Haematoxylin and eosin. ×14
B. Temporal edge of macular hole. Note rounded edge. Haematoxylin and eosin. ×224
C. Nasal edge of macular hole. Haematoxylin and eosin. ×224

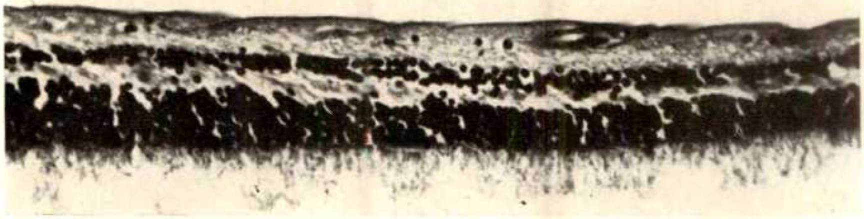

FIG. 4 *Retina on nasal side of left eye. Note loss of ganglion cells and diffuse thinning of inner nuclear layer. Haematoxylin and eosin.* ×224

(Fig. 5, overleaf, p. 236). Some of the nuclei in the inner nuclear layer had a washed-out, vacuolated appearance. In addition, there were numerous small empty spaces in this layer (Fig. 6, overleaf, p. 236).

Trypsin digests of both retinae demonstrated preservation of retinal capillaries, their endothelial cells and intramural pericytes (Fig. 7, overleaf, p. 237). There were a few strands representing degenerated capillaries.

OPTIC PATHWAYS

The optic nerves, chiasm, and tracts showed almost complete loss of myelin and axis cylinders (Fig. 8, overleaf, p. 237).

Only rare axis cylinders remained in these areas. There was marked proliferation of astrocytes and their fibres, and fibrosis of reticular spaces around intraneural blood vessels and in the arachnoid.

Both lateral geniculate bodies were shrunken to 3/4 of the diameter of a normal control. The laminar pattern of their cells was well preserved (Fig. 9, overleaf, p. 238). All laminae were diminished in size. There was some decrease in number of nerve cells in all laminae, but cell density was increased in laminae 3 to 6. Nerve cells were shrunken in all laminae (Fig. 10, overleaf, p. 238). The Nissl substance of the nerve cells was unremarkable. Nerve fibres in the lateral geniculate bodies were decreased in number. Marked proliferation of fibrillary astrocytes was present (Fig. 11, overleaf, p. 239).

Cells of the various laminae in the central vision projection areas of the left lateral geniculate body were measured in 15-μ paraffin-embedded coronal sections. The means of the longest and shortest

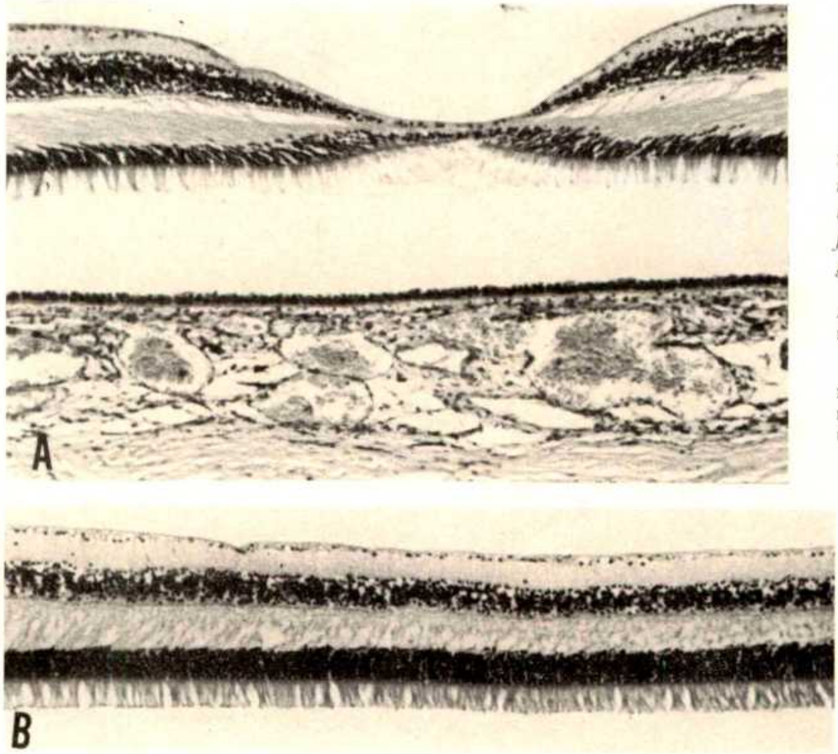

FIG. 5 *Retina of right eye, showing extreme thinning of nerve fibre layer and loss of ganglion cells.*

A. Macula. Haematoxylin and eosin. ×56

B. Retina near macula. Haematoxylin and eosin. ×56

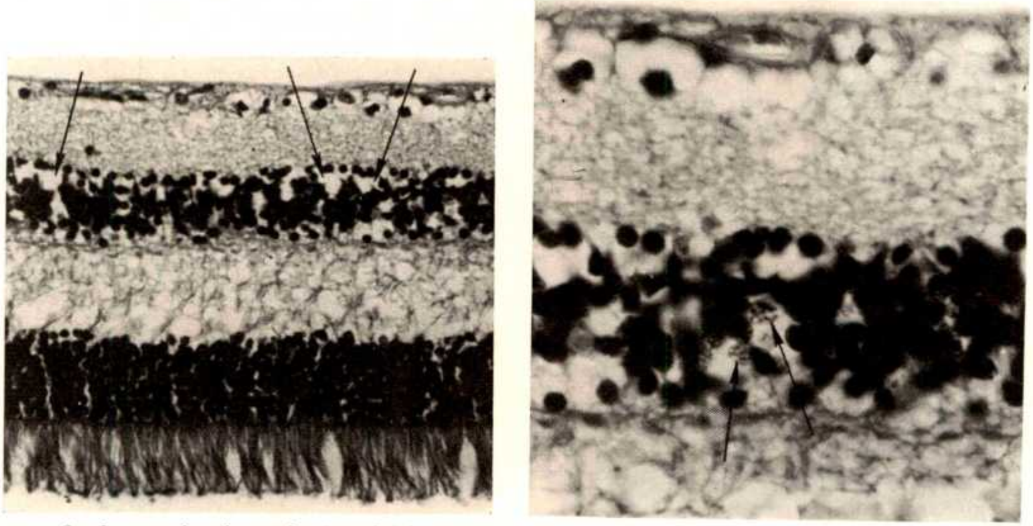

FIG. 6 *Inner nuclear layer of retina of right eye*

A. Multiple cystic spaces (arrows). Haematoxylin and eosin. ×240

B. Nuclei with washed-out vacuolated appearance (arrows). Haematoxylin and eosin. ×600

diameters of thirty cells in each lamina, measured by means of a screw micrometer eyepiece, were compared with a normal control from a slightly older man (Table, overleaf, p. 239). Shrinkage of cells to between 74 and 87 per cent. of normal was observed. The measurements of Chacko (1949) are presented for comparison.

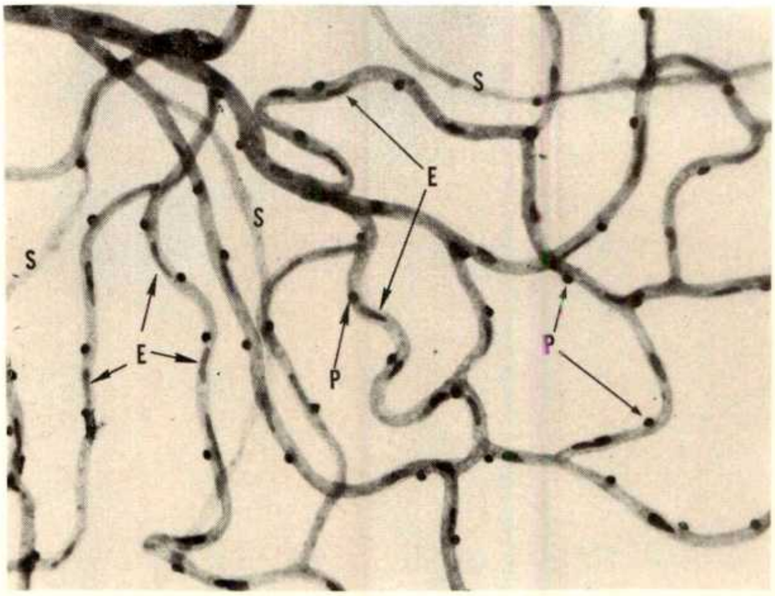

FIG. 7 *Trypsin digest preparation of retina, showing preservation of capillaries, endothelial cells (E), and intramural pericytes (P). Only a few acellular strands (S), representing degenerated capillaries, are seen. Right eye. PAS.* × 214

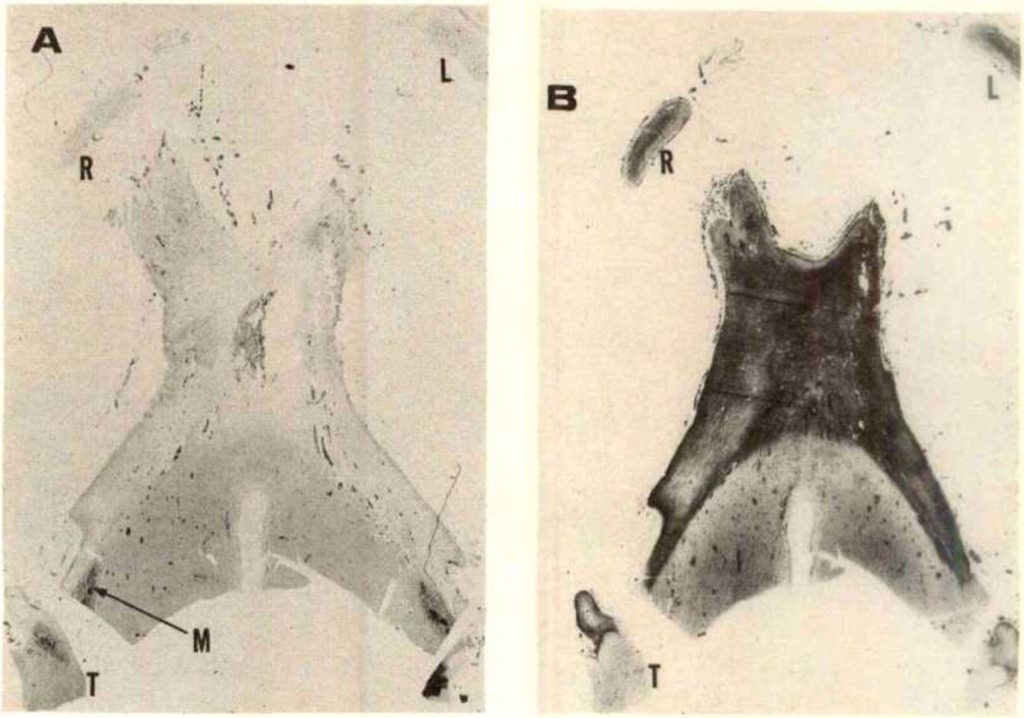

FIG. 8 *Optic nerves, chiasm, and tracts, showing total loss of myelin and severe gliosis. Normal myelin staining (M) is seen in hypothalamus. Cross-section of flattened right (R) and left (L) optic nerves. Cross-section of right optic tract (T).*

A. Combined PAS–Luxol fast blue for myelin. ×5

B. Holzer for glial fibres. ×5

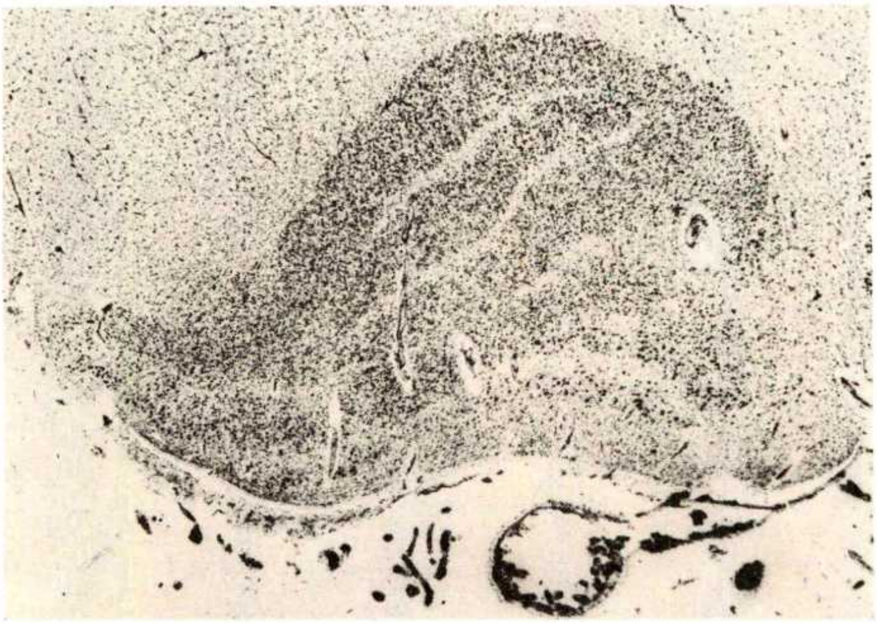

FIG. 9 *Coronal section of left lateral geniculate body. Shrinkage of lateral geniculate body as a whole and increased cellularity. Nissl,* 15µ. ×22·5

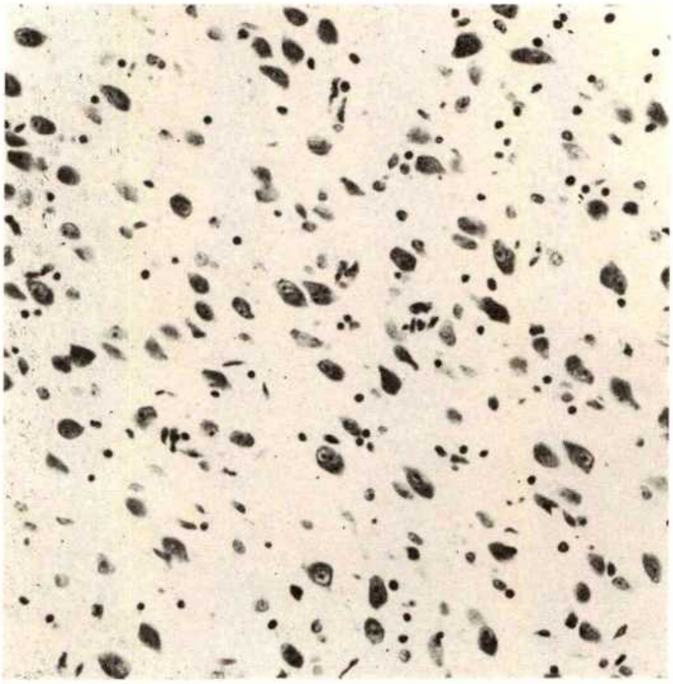

FIG. 10 *Higher power view of lamina* 3 *of left lateral geniculate body. The nerve cells are atrophic and the nerve and glial cells increased in number. Nissl stain,* 6µ. ×260

Both geniculo-calcarine tracts had slight proliferation of astrocytes and some rarefaction of nerve fibres. The visual cortex showed no specific changes.

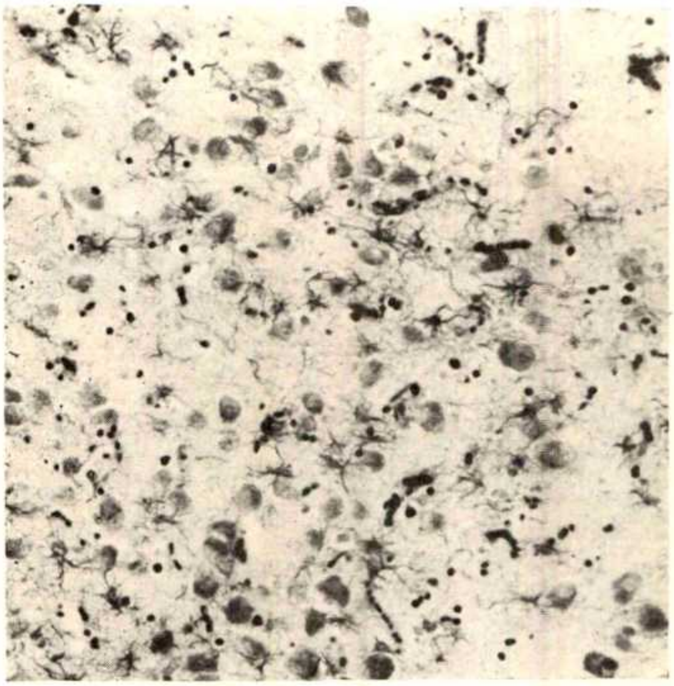

FIG. 11 *Astrocytes, showing proliferation and formation of fibres in lamina* 3 *of left lateral geniculate body. Holzer stain,* 10μ. ×260

Table *Cells of lateral geniculate body. Means of diameters of cells in microns (with standard deviations) in different laminae in central vision area*

Lamina	*Present Case*	*Control**	*Chacko* (1949)
1	17·8 ± 3·8	23·0 ± 3·9	23·1
2	20·0 ± 3·0	24·0 ± 3·4	24·0
3	14·2 ± 1·7	17·0 ± 2·0	18·9
4	14·3 ± 1·8	16·8 ± 2·0	17·1
5	14·3 ± 2·2	19·4 ± 3·2	15·9
6	15·2 ± 1·6	17·5 ± 2·3	14·7

*52-year-old male

Comment

(*a*) *Antegrade degeneration*

Antegrade trans-synaptic degeneration of neurons is well exemplified in degeneration of cells in the lateral geniculate bodies after the enucleation of an eye.

Goldby (1957) studied the lateral geniculate bodies of a 59-year-old man who died 36 to 40 years after enucleation of one eye. He observed considerable shrinkage of each affected lamina compared with the corresponding normal lamina of the opposite side. Cell density was approximately the same in the atrophic as in the normal laminae, but the remaining cells of the atrophic laminae exhibited a diminution in the size of the perikaryon of the neurons and a variable loss of Nissl granules. Glial proliferation was also observed.

Kupfer (1965), however, studying transneuronal atrophy in the lateral geniculate nuclei of seven patients, noted no apparent increase in the number of glial elements in atrophied laminae as compared qualitatively with normal laminae. He observed no indication of loss of neurons in the atrophied laminae before 2 years had elapsed after unilateral enucleation. After longer periods of time, cell loss did occur.

In spite of the abundance of reported cases showing antegrade trans-synaptic degeneration of the lateral geniculate bodies in cases of unilateral optic nerve involvement, cases of bilateral optic nerve involvement are lacking. This may be partially explained by the difficulty of evaluating the lateral geniculate body when the selective laminar atrophy seen in unilateral cases is missing. Shrinkage of the lateral geniculate bodies as a whole was the most distinguishing feature. Although the density of the cells was increased, the total number of neurons was decreased and there was a reduction in size of the perikaryon of the remaining neurons.

Gliosis of the lateral geniculate bodies was another prominent feature of this case. Precise measurements may be impossible because the stretching of paraffin-embedded brain tissue which usually occurs in processing may be reduced by the gliosis. It is also conceivable that loss of nerve fibres entering from the optic tracts may play a major role in the shrinkage of the lateral geniculate bodies. The gliosis seen in the lateral geniculate bodies could be largely an extension of the optic tract gliosis rather than entirely reactive gliosis secondary to loss of nerve cells.

Slight reduction of nerve fibres in the geniculo-calcarine tracts secondary to the loss of neurons in the lateral geniculate bodies is another feature of the antegrade trans-synaptic degeneration.

(b) *Retrograde degeneration*

Van Buren (1963) demonstrated experimentally antegrade and retrograde trans-synaptic degeneration in three monkeys. In two of the animals section of the optic chiasm was followed by degeneration of layers 1, 4, and 6 of the lateral geniculate bodies (antegrade trans-synaptic) and extensive loss of ganglion cells in the nasal side of the retinae. The retrograde degeneration crossed the synapses between the ganglion cells and bipolar cells, as shown by cystic changes in the inner nuclear layer. The time interval was 20 months. In the third animal 4 years after ablation of the right occipital lobe there was marked atrophy of the lateral geniculate body on the same side (retrograde degeneration), shrinkage of the right optic tract to 44 per cent. of the cross-sectional area of the left, and loss of ganglion cells on the right side of the fovea of both eyes (trans-synaptic retrograde degeneration).

The slow progress of degeneration of the central stump of a severed axon as compared to the peripheral stump (Wallerian degeneration) has long been recognized (Cole, 1968). The central stump may undergo a more subtle but definite atrophy. The astrocytic and microglial reaction accompanying Wallerian degeneration stands in marked contrast to the paucity of reaction in the central stump.

For degenerative changes to appear in the neuron preceding the injured one in the pathway of the impulses (trans-synaptic retrograde degeneration) much longer periods of time are undoubtedly required. Van Buren (1963) postulated the presence of a feedback system as the explanation for retrograde degeneration across a synapse. Wolter and Lund (1968) presented evidence for centrifugal fibres in the nerve-fibre layer of the retina. Altered activity in these might play a role in degeneration of cells in the inner nuclear layer.

Numerous reports of retrograde degeneration in the visual pathways occurring in man have been well summarized by Gills and Wadsworth (1967). These include optic atrophy after long-standing occipital injury, loss of retinal ganglion cells in patients with tumours of the optic chiasm and tracts, and complete absence of ganglion cells and signs of degeneration in some cells of the inner nuclear layer in a patient with an optic nerve tumour. In the last case the electroretinogram was essentially normal despite total amaurosis for more than 5 years.

Kupfer (1963) commented that within 6 months a lesion of the optic nerve fibres at the level of the chiasm results in retrograde degeneration of the corresponding retinal ganglion cells. Cell degeneration, he postulated, ensues because of lack of collaterals from the main axon trunk.

Gills (1966) noted larger electroretinographic responses in eyes of two humans with sectioned optic nerves than in their companion eyes, supporting the concept of centrifugal fibres in the optic nerve that may be inhibitory.

In nine autopsied eyes with lesions of the optic nerve of more than 2 years' duration, Gills and Wadsworth (1967) observed a significant reduction in the cellularity of the inner nuclear layer. They pointed out the possibility that inner-layer nuclear changes might be a consequence of a secondary or tertiary mechanism rather than any direct effect on the connecting neuron by the degenerating ganglion cell.

Retrograde degeneration in our case is most readily demonstrated by the absence of retinal ganglion cells. Cross-sections of the optic nerves 9 and 16 mm. posterior to the globes also showed severe atrophy. Retrograde trans-synaptic degeneration was indicated by the reduction in cellularity of the inner nuclear layer, especially in the left eye, and possibly the empty spaces and vacuoles in the inner nuclear layer of the right eye. Similar empty spaces are present but much less conspicuous in the thinned inner nuclear layer of the left eye. It is difficult to be certain, however, that these empty spaces and vacuolated nuclei were not due to *post mortem* changes rather than to true degeneration. They were similar to the cystic changes observed in the monkey reported by van Buren (1963) and the human case reported by Gills and Wadsworth (1967). The retrograde changes, as expected, were not accompanied by gliosis.

The left eye, in addition, contained a zone of severe retinal thinning, a chorioretinal scar, and a macular hole. We believe these findings, not present in the right eye, can be accounted for as follows: on the side of entry of the bullet a much greater effect was undoubtedly produced on the orbital tissues than on the opposite side where the bullet came to rest adjacent to the optic canal. The path of the bullet came much closer to the left eye than to the right. A concussion wave travelled through the semi-fluid orbital contents. The concussion effect on the left eye resulted in retinal oedema and ultimately in the structural changes noted above.

The exact cause of blindness must remain partly unexplained, since neither optic nerve was mechanically trans-sected. The concussion effect of the bullet as it passed beneath the left optic nerve and came close to the right optic nerve may have produced its damage in various ways: tearing of axons; compression of axons by oedema or haemorrhage into the optic nerve meninges or the nerve itself; ischaemia from tearing of small pial vessels or vessels within the nerve itself (Duke-Elder, 1954). The result was immediate total and permanent blindness.

The finding of an intact retinal vascular pattern as demonstrated by trypsin digestion may seem surprising in view of the long-standing degeneration of the inner retinal layers. It is consistent, however, with the conclusions of Gerstein and Dantzker (1969) and Dantzker and Gerstein (1969) that vascular degeneration occurs after exposing the retina to procedures which are destructive to the outer cell layers. The resulting proximity of the choroidal capillaries to the inner layers leads to an increased oxygen tension which has a vasoconstrictive and degenerative effect on the retinal microvasculature.

Henkind, Charles, and Pearson (1970) likewise found normal cellularity of digest preparations in a patient who had ischaemic optic neuropathy with retrograde degeneration of ganglion cells in one eye.

We cannot rule out transient spasm of the central retinal arteries as a possible contributory factor in the retinal findings of our case. Reinecke, Kuwabara, Cogan, and Weis (1962) demonstrated experimentally that retinal changes produced by ischaemia in the cat for periods less than 1½ hours were reversible. After longer periods of retinal ischaemia the digest preparations eventually showed a network of acellular capillary strands. Endothelial cells and intramural pericytes had virtually all disappeared.

Summary

A 45-year-old man had been totally blind following a gunshot wound which injured both optic nerves nearly 13 years previously. *Post mortem* examination revealed degenerative changes in the injured neurons (retinal ganglion cells and distal and proximal stumps of their axons) as well as antegrade trans-synaptic degeneration (lateral geniculate body) and retrograde trans-synaptic degeneration (inner nuclear layer). A macular hole and a chorioretinal scar were also present in one eye. The retinal vascular pattern remained intact.

We wish to express our appreciation to Charles E. Corcoran, M.D., for providing the clinical history and to Gleb H. Budzilovich, M.D., for help in interpreting neuropathological findings.

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Atavistic ocular ossicle

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Metaplastic ossification frequently follows ocular scarring. Anterior scleral ossicles are normal in most common fish, *e.g.* dogfish, and in reptiles, and are said to have accommodative and protective functions. Birds (219 out of 532 species: Tiemeier, 1950) have an os opticus of highly cancellous texture lying in the posterior sclera and surrounding the optic nerve head in one or several places. Duke-Elder (1958) wrote that "no satisfactory theory for its presence has been put forward". He also mentioned the occurrence of "fatty tissue, cartilage, and even bone" in coloboma of the vitreous in microphthalmic eyes (Duke-Elder, 1964). This description may refer to cases now being recognized as examples of the 13–15 trisomy syndrome. Saraux and Dhermy (1968) found a nodule of well-developed bone in the line of a uveal coloboma but located episclerally near the optic nerve. This was present in a case of D-trisomy with translocation.

This paper reports a case of congenital isolated posterior intrascleral ossification, which appears to be a unique finding.

Clinical history

A married woman aged 23 years was delivered at full term of her first baby on May 25, 1969. She had had "tablets" for hyperemesis gravidarum in the first trimester and apart from an *E. coli* pyelitis, the antenatal history was uneventful. She was blood group O RH+. The Wassermann reaction and Venereal Disease Reference Laboratory tests were negative. There was no family history of ocular disorder. The baby girl, delivered by vacuum extraction and weighing 3·3 kg., was admitted to the Special Care Unit where she was found to have a left facial palsy and bilateral colobomata. She died 48 hours later after repeated convulsions. Skull and lateral spinal *x* rays, urinary chromatography, and karyotyping gave normal results. Laboratory tests showed evidence of urinary infection and the serum had low calcium, raised phosphorus, and normal electrolyte levels.

Pathology

AUTOPSY FINDINGS

The baby weighed 3 kg. The cranium and face appeared to be normally formed except for atypical dysplasia of the left auricle, which had a large flat helix with a single layer pointing upwards and an absent lobe. The right ear was large but had a tiny lobe. The eyes appeared to lie within normal orbital fossae. No congenital defects were found in the other systems. The cause of death was bilateral bronchopneumonia.

Macroscopical examination

The left eye measures 20 × 19 × 18 mm. with an indefinite cornea of approximately 10 mm. diameter and an inferior nasal iris coloboma. The opened specimen shows a

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typical but irregularly-shaped coloboma involving the retina and uvea and extending just to include the disc.

The right eye measures 19 × 18 × 17 mm. The corneal diameter is 9 mm. and the anterior aspect shows an inferior nasal coloboma. The opened specimen shows an irregular coloboma of the uvea and retina extending above the disc, which is itself abnormal. The total area involved by maldevelopment is greater than in the left eye.

The external ocular muscles appear to be normally developed on both sides.

Microscopical examination

The left eye shows no abnormality of the cornea. The coloboma involves the iris, ciliary body, retina, and choroid in varying degrees, with the conventional histology seen in this defect. The iris tissue near the coloboma shows persistence of a primitive type of mesoderm. The lens appears to be normal. There is slight ectasia of the sclera along the line of the embryonic fissure, and about 3 mm. from the optic disc there is a focus of cartilage proceeding to ossification (Figs 1 and 2) lying encased by scleral mesoderm at all levels. The normal constituents of bone are present with osteoid tissue, osteoblasts, an occasional osteoclast, Haversian canal systems, and scattered normoblasts (Fig. 3). The globe has been serially sectioned and the ossicle measures 0.3 mm. in thickness. No choroidal elements have formed in this area and the inner scleral layers covering the bone are in direct contact with attenuated retina which has an occasional rosette-like formation. Myelination of the optic nerve is normal for the age of the infant.

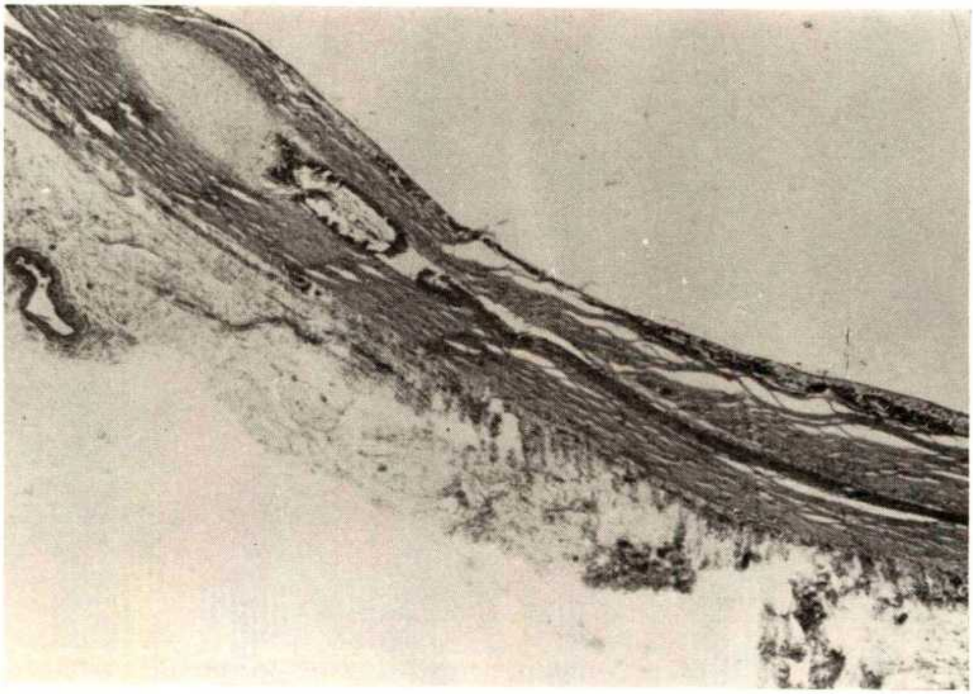

FIG. 1 *Intrascleral chondro-ossification in uveal coloboma with overlying attenuated dysplastic retina. Haematoxylin and eosin.* × 8

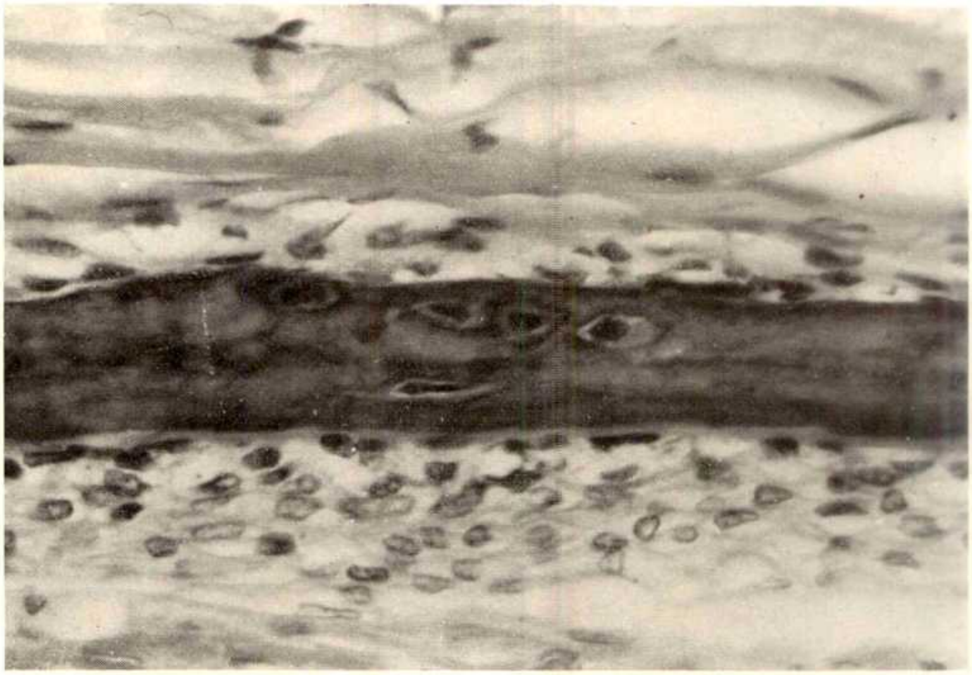

FIG. 2 *Area of dense compact bone and periosteal-type cells. Haematoxylin and eosin.* × 330

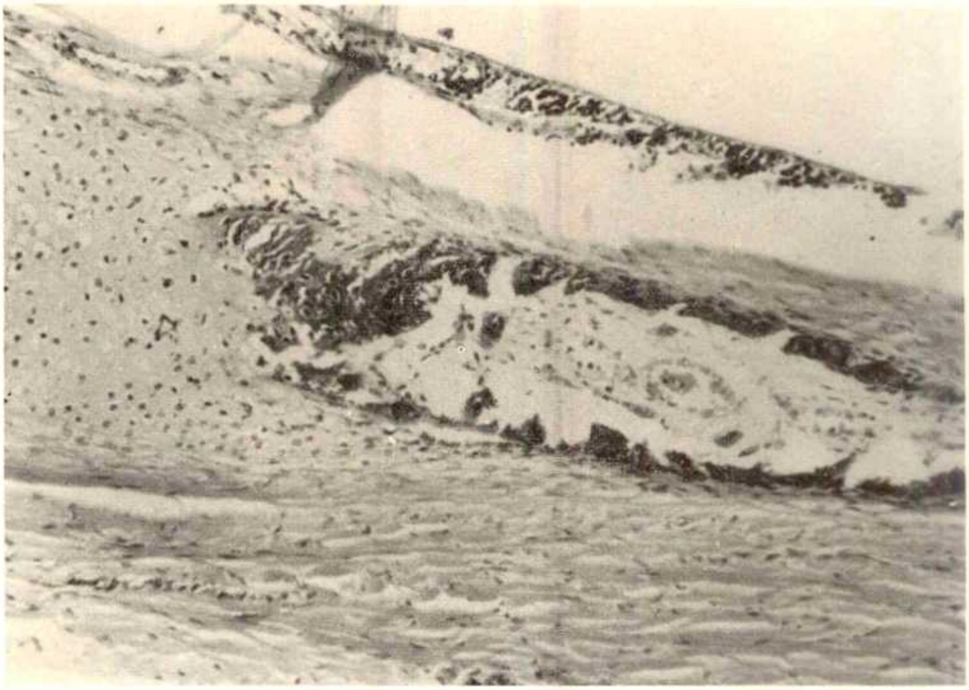

FIG. 3 *Ossifying zone with an osteoclast and marrow formation. Haematoxylin and eosin.* × 85

The right eye shows scleralization of the cornea which is otherwise normal. The coloboma involves the iris, ciliary body, choroid, and retina to varying degrees. The choroid has failed to develop in the posterior part of the embryonic fissure and this defect extends across the optic disc to the macula. The lens is not remarkable. The iris shows irregular hyperplasia of the pigment layer, particularly at its root. Dysplastic retinal tissue lies in direct contact with ectatic sclera and shows focal herniation of retinal elements into orbital fat. A coloboma of the optic disc is associated with excavation of the sclera, the lumen of the cavity being filled with whorls and fasciculated optic nerve fibres. These fibres are degenerate and show corpora amylaceae. No cartilaginous or bony elements have been found on serial sectioning. The optic nerve is not remarkable.

Comment

Colobomata of the eyes, microphthalmos, and anomalies of the ears have been described in association with paralysis of the VIIth nerve. This is said to be due to central atrophy of the nucleus (nuclear aplasia: Möbius, 1892). It is possible that the present case is a variant of Möbius's syndrome.

Intracartilaginous ossification occurred in the sclera of this eye. Cartilage is normally present in the posterior sclera of certain fish and reptiles. It is found in the severely microphthalmic colobomatous eyes of the 13–15 trisomy syndrome, its location being in the anterior para- or retrolental area near the coloboma. Manschot (1958) mentioned the presence of retrolental cartilage in a case of persistent hyperplastic vitreous. Yanoff and Font (1969) found cartilage in the vitreous in unilateral microphthalmos in a normal 4-year-old girl, and Garner and Griffiths (1969) reported bilateral cartilaginous plaques in anterior staphylomatous tissue in a foal. Published papers to date have shown cartilage in the anterior half of the globe in the human eye. Dhermy (1970), however, found an intrascleral island of cartilage between a scleral coloboma and the optic nerve in a case of a ring-13 chromosome.

As far as can be ascertained no case similar to the one now presented has been described. The cause of the scleral ossification in the left eye could be sequestration of a focus in the embryonic fissure from the neighbouring orbital chondrocranium. It appears to be more likely, however, that the primitive mesenchyme forming the sclera had undergone heteroplastic changes, *i.e.* a primary anomalous differentiation in the developing tissue. The paraxial mesoderm which forms the scleral coat extends from the limbus to reach the posterior pole at the 5th month of intrauterine life. Thus the ossification can be presumed to have occurred during the last 4 foetal months. The proximal end of the embryonic fissure failed to close in the right eye but no bone or cartilage was found.

Having regard to the points of similarity between the scleral bone in the present case and the os opticus of lower species, it is tempting to call it an atavistic ossicle.

Summary

Isolated posterior intrascleral ossification in a colobomatous eye is described in a full-term infant with normal karyotype. Death occurred 48 hours after delivery. The formation of such an ossicle is thought to be a unique occurrence.

We wish to acknowledge the help of Dr. E. Dillon, who performed the autopsy, Dr. J. Masterson for karyotyping, and Mr. R. Lester, F.I.M.L.T., for technical aid.

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Retinal haemorrhages in newborn infants

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Although neonatal retinal haemorrhage is a common pathological finding in about 20 per cent. of newborn infants, the cause of this condition is still not well understood.

Jäger (1861) is generally accepted as the first author to have reported the condition. Estimates of its incidence have varied from 2·6 to 50 per cent. (Duke-Elder and Dobree, 1967). Chace, Merritt, and Bellows (1950), in a study of more than 1,000 newborn infants, found retinal haemorrhages in 2·6 per cent.; Belmonte González (1947) in 27·4 per cent. of 124; Cavrot (1956) in 20 per cent. of 421; Kauffman (1958) in 18·2 per cent. of 7,727; Giles (1960) in 40 per cent. of 100 infants.

The types of retinal haemorrhage have been described by many authors, including Mezey (1952) and Schenker and Gombos (1966). They were classified by Richman (1938) into four groups:

(a) Flame-shaped;
(b) More or less circular in the deeper layers of the retina;
(c) Sharply circumscribed, perfectly round, and deep red;
(d) Subhyaloid.

Many possible causes have been suggested. Schleich (1884) thought they were due to increased venous pressure within the cavernous sinus with congestion of the ophthalmic veins. Naumoff (1890) found retinal haemorrhage in a patient with compression of the central retinal vein. Ehrenfest (1922) stated that a haemorrhagic diathesis was present in infants who manifested retinal haemorrhages at birth. Pietrowa (1956) attributed them to vitamin K deficiency. Chace and others (1950), Musini and Grassi (1950), and Singer, Sgallova and Kudrnovsky (1956) thought that prothrombin deficiency was the cause.

On the other hand, most investigators (Schleich, 1884; Paul, 1900; Lemmingson and Stark, 1957; Sanchez Ibañez, Belmonte González, and Navarro Martinez, 1963) suggested that they resulted from obstetric trauma. Krauer-Mayer (1966) found 50 per cent. and Neuweiler and Onwudiwe (1966) 72 per cent. in cases of forceps delivery in which ophthalmoscopic examination had been performed within 24 hours after birth.

Material and methods

In this study, 1,238 newborn infants were examined in the Department of Gynaecology and Obstetrics of the Faculty of Medicine at Istanbul University. One hour after the instillation of 5 per cent. homatropine solution, Sauer's speculum was inserted for the examination of the infant's eye and the Jena ophthalmoscope was used for fundus examination, the head being held by a nurse.

709 were seen within the first 24 hours after birth, 304 within 25 to 48 hours, and 225 between the 3rd and 5th day. All infants with retinal haemorrhages were examined at approximately 24-hr intervals and were followed until the haemorrhages disappeared.

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The mother's age, parity, illness before or during pregnancy, premedication, technique of delivery, duration and stages of labour, time of rupture of the foetal membrane, prematurity, and the Apgar score of the infant, were all recorded.

In twenty newborn infants with retinal haemorrhages, the prothrombin time was measured by Quick's method.

Results

The incidence of retinal haemorrhage varied according to the time of examination. Those undertaken within the first 24 hrs revealed an incidence of 18·9 per cent. in 709 cases; between the 2nd and 3rd day in 12·5 per cent. of 304 cases; and between the 3rd and 5th days in only 2·6 per cent. of 225 cases (Table I).

Table I *Relationship between time of examination and percentage of retinal haemorrhages*

Hours after birth	*Percentage in which retinal haemorrhage occurred*
1–24	18·9
24–48	12·5
72–120	2·6

Of the 1,238 newborn infants examined, 178 (born to 175 mothers) were found to have retinal haemorrhages.

MOTHER'S AGE

The 175 mothers were divided into three age groups; under 20, 20 to 30, and over 30 years; 36 mothers of affected infants (20·6 per cent.) were found to be over 30 years of age while in the corresponding control group there were only nineteen (10·9 per cent.).

The comparison between cases and controls for each group is shown in Table II ($\varepsilon = 2{\cdot}2$; $0{\cdot}22 < \alpha < 0{\cdot}03$).

Table II *Percentage of neonatal retinal haemorrhages in relation to mother's age compared with controls**

Mother's age (yrs)	*Mothers in whose infant haemorrhage occurred*		*Controls*	
	No. of cases	*Per cent*	*No. of cases*	*Per cent.*
Under 20	40	22·9	39	22·3
20–30	99	56·5	117	66·8
Over 30	36	20·6	19	10·9
Total	175	100	175	100

* Controls comprised 175 mothers matched for parity

PARITY

In the 175 mothers of affected infants, there were 81 primiparae (46·4 per cent.) and 94 multiparae (53·6 per cent.). The difference between these figures and the group as a whole was significant ($P < 0{\cdot}001$), retinal haemorrhages being more commonly seen in the babies of primiparae (Table III).

Table III *Parity and occurrence of retinal haemorrhages*

Parity	*Primiparae*		*Multiparae*		*Total*	
	No. of cases	*Per cent.*	*No. of cases*	*Per cent.*	*No. of cases*	*Per cent.*
Mothers in whose infants haemorrhage occurred	81	46·4	94	53·6	175	100
Total cases	406	33	832	67	1,238	100

ILLNESS BEFORE OR DURING LABOUR

One case of multiple sclerosis, one of asthma, two of heart disease, and five of eclampsia or pre-eclampsia were recorded.

DELIVERY TECHNIQUE

The greatest number of retinal haemorrhages occurred in infants delivered by vacuum extraction, 25 out of 62 (40·3 per cent.) being recorded. Of nine delivered with the aid of forceps three showed retinal haemorrhages (33·3 per cent.). By contrast, in 125 cases of Caesarean section, there was only one case of retinal haemorrhage (0·8 per cent.).

1,042 cases were delivered spontaneously; of these 147 cases exhibited retinal haemorrhages (14·2 per cent.).

PREMEDICATION

In twelve of the 175 mothers of affected children pituitary extract had been used to accelerate the delivery.

DURATION OF LABOUR

In sixty of the 175 mothers of affected children the duration of the second stage of labour was prolonged; in 23 the total duration of labour was prolonged but in four of these the second stage was shortened.

PREMATURITY

61 of the 1,238 deliveries were premature, and retinal haemorrhages were recorded in fifteen (24·6 per cent.) of these infants.

APGAR SCORE

This was accepted as a criterion for asphyxia of the newborn. In 131 cases, the score was recorded as normal (10 or 9); and in 47 as lower than normal (less than 9).

PROTHROMBIN TIME

This was measured by Quick's method. Of twenty affected infants, four had severe and ten moderate prolongation of the prothrombin time (Table IV, opposite).

Table IV *Prothrombin time measured by Quick's method in twenty cases with retinal haemorrhages*

Case no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Prothrombin time (sec.)																				
Normal	12	12	12	12	12	13	13	13	13	13	13	13	13	13	16	17	12	12	12	12
Measured	13	13	50	15	17	13	14	13	13	17	16	14	13	16	16	17	12	25	13	24

Type, density, and duration of retinal haemorrhages

(1) FLAME-SHAPED

These occurred everywhere in the fundus except at the extreme periphery. They were seen mainly at the disc area or towards the periphery along retinal vessels. They were bright red in colour and of varying density. They were rare in the macular area. In some cases they occurred first at the disc border or at the bifurcation of the central retinal vein.

They occasionally disappeared within 24 hours, usually within 3 days, and sometimes remained as long as 5 days.

(2) WIDE, VERY BRIGHT RED, IRREGULAR, AND SUPERFICIAL

These were thought to originate from superimpositions of flame-shaped haemorrhages and occurred in the same areas.

(3) ROUND, RED, AND DEEP

These were rarer and occurred mostly at the posterior pole. From the topographical point of view there was no relationship between these haemorrhages and the retinal vessels. Occasionally they occurred even in the macular area.

They usually disappeared after 14 to 21 days. In one case a haemorrhage of this type, which was situated on the macula, disappeared 6 weeks after birth leaving no ophthalmoscopic damage.

In the investigation of the aetiology and density of all types of retinal haemorrhage the following case provides a very good example.

Case report

A woman aged 39 *years*, a multipara, was admitted to hospital in April, 1968. The foetal membrane ruptured spontaneously 7¼ hours after onset of rhythmic uterine contractions. The second stage of labour was prolonged to 3¾ hours (usual duration for multiparae 1 hour or less); the heart sounds of the foetus became arrhythmic many times during labour, signifying asphyxia. Pituitary extract was given and labour was completed successfully. The Apgar score of the infant was 5, and it died 12 hours after because of intolerable asphyxia. An ophthalmoscopic examination was made and fundus photographs were taken 2 hours before death. The right and left fundi were full of haemorrhages with marked oedema and the retinal vessels were congested. The appearance of the fundi was very similar to that of central retinal vein thrombosis.

Discussion and conclusion

The variety of percentages given in the literature for the incidence of neonatal retinal haemorrhages seems to be related to the time of examination after birth. This study showed (Table I) that the later the time of examination the fewer retinal haemorrhages were found.

In primiparae, especially in older women, rigidity of the neck of the uterus and resistance of the pelvis to delivery are greater than in multiparae. If there is any connection between obstetric trauma and neonatal retinal haemorrhages, as suggested by some authors, the incidence of retinal haemorrhages should be higher in primiparae. This is confirmed by our findings (Tables II and III).

Similarly a higher percentage was found in cases of vacuum extraction (40·3 per cent.) and a low percentage after Caesarean section (0·8 per cent.).

Kauffman (1958) emphasized that either very short or very prolonged labour would give rise to retinal haemorrhage in the infant. In the first instance this is due to a sudden decrease of venous pressure, and in the latter to increased pressure in the intracranial veins. In this study, sixty of 178 cases of retinal haemorrhage were associated with a prolonged second stage of labour, and four with a shortening of total labour time.

It has been suggested by Cavrot, Humblet, and Richard (1955) that the fragility of the bloodvessels is higher than normal in infants whose birth weight is below 3,000 g., and Ayberk (1954) reported that the incidence of retinal haemorrhages was higher in premature than in full-term infants. In this series, 24·6 per cent. of 61 prematures showed retinal haemorrhages, while the total percentage was 14·3. On the other hand, Kauffman did not find that prematurity was associated with retinal haemorrhages.

Cavrot (1956) reported that retinal haemorrhages due to increased fragility of the blood vessels could be treated by using a "nontoxic antifragility substance", of vit. B, vit. K, vit. E, rutine, and hesperidine. He found that the average incidence of retinal haemorrhage in the newborn infant was 34 per cent. in untreated controls, but only 7 per cent. in those in which this substance had been given to mothers. Pray, McKeown, and Pollard (1941) observed that the incidence of retinal haemorrhages was reduced in infants of mothers treated with a vit. K preparation during or before labour. Nevertheless, Kauffman (1958) found that the incidence of phlebitis was increased in mothers who had been treated with vit. K. Millan, Ady, and Beltron (1950) and Singer and others (1956) suggested that the insufficiency of the blood-clotting mechanism of the newborn infant might increase the incidence of retinal haemorrhage. Of twenty cases investigated, four showed severe prolongation of prothrombin time, ten showed moderate prolongation, and six were normal.

The major factor in the pathogenesis of retinal haemorrhage, however, has been shown by this study to be foetal circulatory disturbance.

Summary

Types of retinal haemorrhage in newborn infants are described and the pathogenesis of such haemorrhages is reviewed with reference to the literature. Of 1,238 newborn infants investigated, 178 (14·3 per cent.) were affected. Examination within 24 hours revealed a percentage of 18·9 but between the third and fifth day the figure was only 2·6 per cent. It is concluded that the later the time of fundus examination the less the incidence of retinal haemorrhage found. Comparative studies of the incidence and aetiology of retinal haemorrhages have shown that the difference between primiparae and multiparae is

significant ($P < 0{\cdot}002$); retinal haemorrhages were more common in the babies of primiparae, confirming the role of obstetric trauma in the pathogenesis of neonatal retinal haemorrhages.

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Orbital tumours in African children

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The differential diagnosis of proptosis in African children poses a bewildering number of possibilities (Davies, 1968). Many of these cases prove to be due to inflammation of neighbouring sinuses or to invasion of the orbit by parasites or fungi. Orbital tumours causing proptosis occur frequently, and a series of sixty cases of proptosis in childhood caused by neoplasms in the orbit is reviewed in this paper.

Materials and methods

The Department of Pathology, Makerere University, Kampala, has for many years provided the only histopathological service available in Uganda, a country of nearly 10 million people. During the period 1964 to 1968 biopsies from approximately 7,000 malignant tumours were studied histologically. This collection is at present under review and during this work it became apparent that a significant collection of orbital tumours had accumulated. Conditions such as pseudotumour, myelocele, and ossifying fibroma, although not strictly speaking neoplasms, are included in this review in those cases in which a biopsy was required to confirm the diagnosis. Sixty cases of proptosis in patients under the age of 16 years were reviewed. Sections from all cases were stained with haematoxylin and eosin. Other stains used as necessary included PAS, Glees Marsland for neural elements, reticulin stains, PTAH, Fontana, and the naphthol AS-D chloroacetate esterase reaction in suspected cases of chloroma.

Results

The diagnoses made in the sixty cases are shown in the Table. There were forty males and twenty females, the male excess being least marked in cases of Burkitt's tumour. Children with Burkitt's tumour were aged between 3 and 15 years (mean 7·3): sixteen male and twelve female.

The youngest patient with chloroma associated with acute myeloblastic leukaemia was a child aged 1 year, but otherwise the ages ranged from 5 to 12 years. The peripheral blood was normal in two cases though the marrow always showed leukaemic changes.

Three of the six patients with orbital myelocele presented before the age of 6 months except for one child first seen at the age of 3 years. Five out of these six patients were males.

Six cases of fibrous dysplasia causing proptosis were seen and again five of the six patients were males; the average age at presentation was 10 years.

Only two out of seventy patients with nasopharyngeal carcinoma (lymphoepithelioma) presented because of proptosis; one was aged 12 and the other 15 years. The commonest presenting sign was that of lymph node enlargement with or without symptoms of nasal obstruction.

Orbital rhabdomyosarcoma is seen fairly frequently in Uganda, but it so happened that, although six cases were recorded in 1963, only one was seen in the period of this survey (1964–1968).

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Table *Diagnoses in sixty cases of proptosis in African children thought to be due to tumour at the time of operation.*

Burkitt's tumour	28
Chloroma	8
Myelocele	6
Fibrous dysplasia	6
Pseudotumour	3
Nasopharyngeal carcinoma	2
Rhabdomyosarcoma	1 case each
Fibrosarcoma	
Haemangioma	
Retinal anlage tumour	
Aesthesioneuroblastoma	
Neuroblastoma	
Malignant neurilemmoma	

Other tumours seen included one case each of malignant neurilemmoma, fibrosarcoma, haemangioma, retinal anlage tumour, and aesthesioneuroblastoma. Metastatic neuroblastoma was seen only once in a 3-year-old child from Busoga District.

Tribal distribution varied with the type of tumour. Both nasopharyngeal carcinoma and anterior myelocele appear to be much more common in Nilotic tribes. Burkitt's lymphoma was seen most commonly in children from the north and north-west of the country and in none from the south-west, thus confirming the well-known geographical variation reported by Burkitt and Wright (1966). Most of the patients with chloroma lived around the city of Kampala, but this is probably due to a selection bias, since the only specialist haematologists and ophthalmologists in the country are to be found there.

Two tumours in this series appear to be unique for the orbit. Retinal anlage tumour, in spite of its name, occurs most frequently in the maxilla, and no case was found in the available literature in which orbital involvement was recorded. Aesthesioneuroblastoma usually presents as a nasal tumour, but in this case symptoms relating to the nose were minimal in a child aged 3 years presenting with proptosis. Details of these two cases are given below.

CASE 1. MELANOTIC NEUROECTODERMAL TUMOUR OF INFANCY (RETINAL ANLAGE TUMOUR)

A 5-month-old male infant of the Bakiga tribe presented with a swelling of the lateral side of the orbit, displacing the eye upwards and medially. On palpation this was woody and hard, and was shown by *x* ray examination to contain flecks of calcium.

At operation a charcoal-grey mass was found infiltrating the zygomatic bone. This was scraped out and no connection was found between the tumour and either the globe or the maxilla. The child did well after the operation and was noted to be in good health 3 months later, but thereafter was lost to follow-up.

Histologically the tumour consisted of epithelial cells of two distinct types arranged in islands in a background of fairly plump spindle cells. Since the mass had been removed piecemeal it was impossible to assess whether any capsule had formed but clinically there was none. Stain for neural fibres (Glees Marsland) proved negative. The smaller and darker epithelial cells were sometimes arranged in alveoli. The larger cells appeared in association with pigment which bleached with hydrogen peroxide and stained positively with Fontana. This pigment was also seen to be scattered throughout the tumour extracellularly. The two types of cell were sometimes seen in close approximation but in no area could any convincing signs of organoid arrangement be found. However, in some areas, the paler cells became elongated and bore some resemblance to the rods of the retina (Fig. 1).

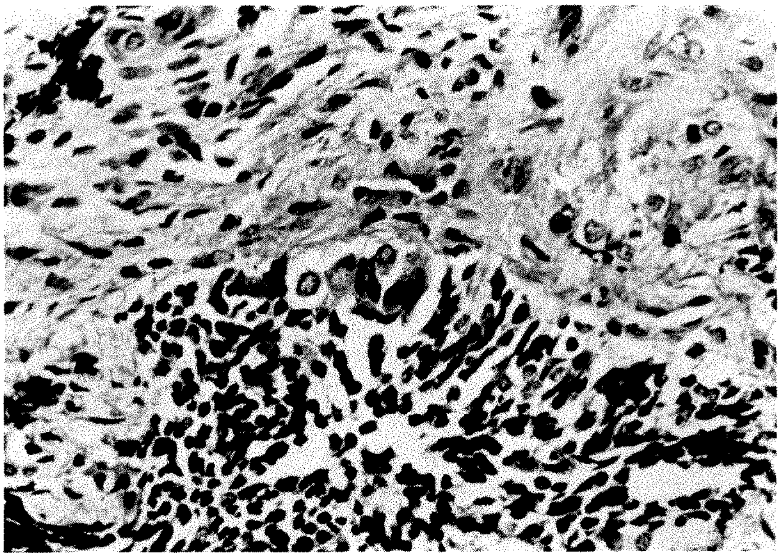

FIG. 1 *Retinal anlage tumour, showing the larger pigmented cells closely approximated to the small neuroblastic cells. A similarity to the rods of the retina may be noted.* × 700

CASE 2. AESTHESIONEUROBLASTOMA

A 3-year-old Muganda female presented with a left-sided orbital swelling which had been present for a few months. The patient did not complain of nasal obstruction and no masses were palpable elsewhere. Chest *x* ray and bone-marrow examination gave normal results. A clinical diagnosis of Burkitt's tumour was made and a biopsy was taken from the orbit. A diagnosis of anaplastic tumour of unknown origin was made at that time and the child was treated empirically with cyclophosphamide. This had no effect after 3 weeks, when the mother and child ran away and have not been seen since.

The diagnosis of aesthesioneuroblastoma was made retrospectively at a slide seminar. The tumour consisted of cells with an epithelial appearance arranged in clumps in a background composed of spindle cells. The spindle cells showed no fibrillary pattern and stains for neural elements were negative. In some clumps the epithelial cells appeared pale and were arranged in an alveolar pattern rather reminiscent of paraganglioma, and elsewhere they were smaller and darker with an organoid arrangement in some parts. Many partially-formed rosettes were seen (Fig. 2, opposite).

Discussion

By far the commonest neoplastic cause of proptosis in childhood in Uganda is Burkitt's lymphoma. The history is much shorter than with many other tumours and is very seldom longer than 3 months. Orbital involvement is seen in about 20 per cent. of children with Burkitt's tumour, but it usually occurs in association with swelling of the maxilla, when it may involve one or both eyes. This association makes the diagnosis fairly obvious clinically. Orbital involvement without clinically apparent swelling of the jaws is seen less frequently and is almost always unilateral. Biopsy is essential for the diagnosis and it

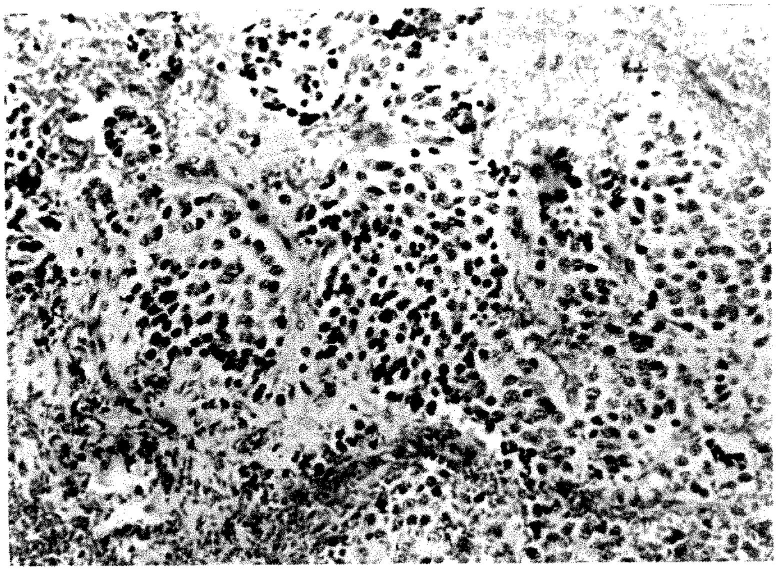

FIG. 2 *Aesthesioneuroblastoma, showing rosette formation and alveolar arrangement of cells.* × 200

is sometimes difficult to obtain satisfactory tissue for standard histological examination (Fig. 3), but touch preparations from very scanty material, even a needle aspiration, will often enable the diagnosis to be confirmed (Fig. 4, overleaf). In the early stages the eye is displaced, but invasion of the orbit is seen only rarely. After prolonged exposure the globe may rupture and in late cases the differentiation from retinoblastoma may be difficult.

The appearance of children with fibrous dysplasia may closely mimic that of Burkitt's

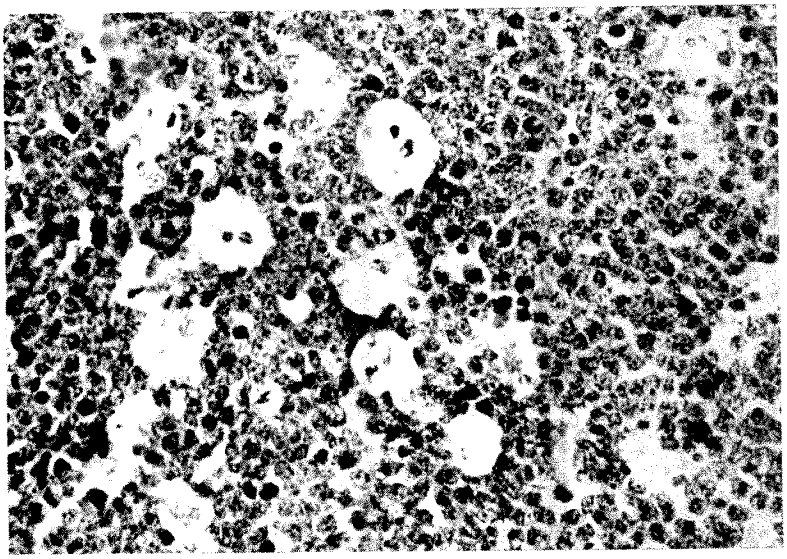

FIG. 3 *Burkitt's lymphoma, showing histiocytes in the tumour which is composed of a homogeneous population of primitive cells.* × 350

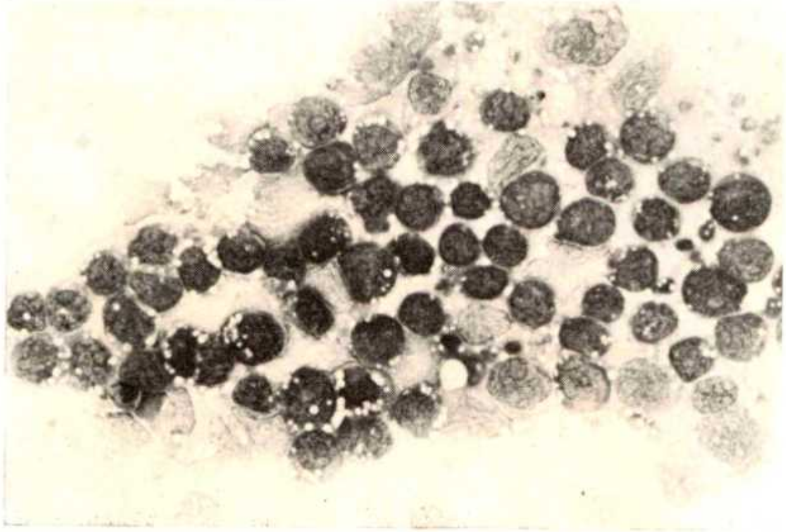

FIG. 4 *Touch preparation of Burkitt's lymphoma showing tumour cells with prominent vacuolation in both nuclei and cytoplasm.* ×900

tumour, but *x* ray studies will usually establish the correct diagnosis. The speckled calcification that occurs in these tumours is virtually never seen in Burkitt's lymphoma.

A more difficult differential diagnosis is that of chloroma. The tendency for acute myelogenous leukaemia to produce orbital swelling has been noted previously (Davies and Owor, 1965). These tumours occur sufficiently frequently to make examination of the bone marrow mandatory in the investigation of any child with proptosis not obviously due to inflammation. The diagnosis of chloroma is sometimes very difficult since the appearance may closely mimic that of histiocytic lymphoma in that the majority of cells are primitive and show abundant pale-staining cytoplasm. If a diligent search is made in such tumours for eosinophilic myelocytes they will usually be found and specific enzyme stains may be used to confirm the diagnosis. The total white count of peripheral blood may be normal in such cases but the marrow almost always shows leukaemia.

Pseudotumours occur most commonly in adults, but three of the twelve examples seen in this 5-year period occurred in children. This fact makes it essential to carry out a biopsy before extirpation is contemplated (Fig. 5).

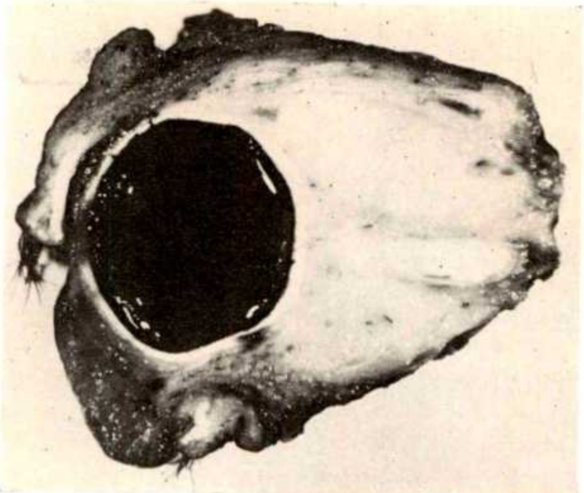

FIG. 5 *Orbital exenteration carried out for proptosis due to a pseudotumour of the orbit*

Proptosis may be due to involvement by nematode and cestode worms and to various fungus infections, such as histoplasmosis duboisii (Fig. 6). The proportion due to such diseases varies in different parts of Africa. Townsend (1962), for example, records that the commonest cause of proptosis in his practice in South Africa was hydatidosis, but no such case was seen by us in Uganda in 5 years.

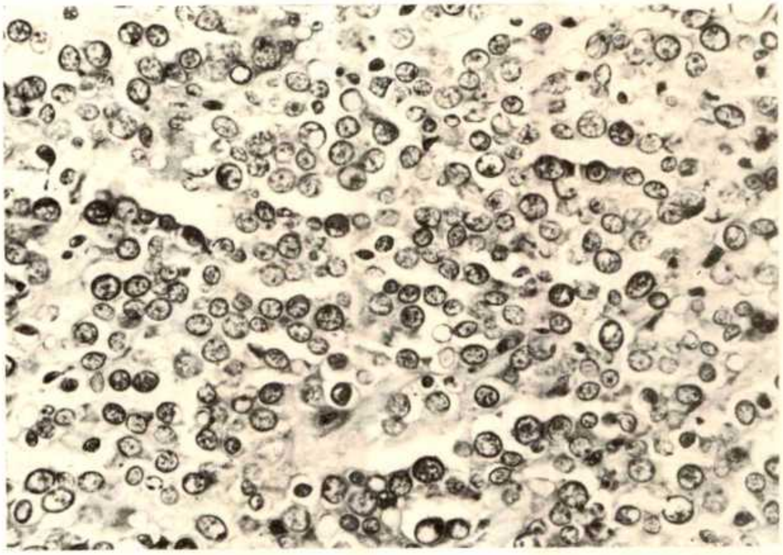

FIG. 6 *Tissue from the orbit of a 6-year-old girl showing innumerable fungal particles of* H. duboisii. ×200

Aesthesioneuroblastoma was first described nearly 50 years ago (Berger, Luc, and Richard, 1924) and for some time seems to have remained largely unrecognized. The differential diagnosis from transitional-cell carcinoma is sometimes difficult to make, and it seems likely that a retrospective review of nasal tumours would discover other examples. More recently many reports have been published and it seems likely that it is, in fact, not uncommon (Castro, de la Pava, and Webster, 1969; Skolnik, Massari, and Tenta, 1966). In previously recorded cases the age at onset has ranged from 9 to 79 years, so that our case is the youngest yet recorded by quite a few years. At the age of 3 years the differential diagnosis from metastatic adrenal neuroblastoma has obviously to be considered, but in this case the organoid arrangement which was a marked feature permitted relatively easy distinction. The finding of fibrillary material in the background tissue is useful confirmatory evidence when present, but it is not mandatory for the diagnosis (Hutter, Lewis, Foote, and Tollefsen, 1963). Most of these tumours present with nasal obstruction usually accompanied by epistaxis. Early involvement of the orbit in this case is probably a result of lack of fusion of the intervening bones. The only other case of aesthesioneuroblastoma seen during this review occurred in a 12-year-old child who presented with nasal obstruction in a rather more typical fashion. This tumour probably arises from the basal plate of the olfactory placode but numerous other sites of origin have been suggested.

The origin of the condition, known by many names including retinal anlage tumour (Halpert and Patzer, 1947) and melanotic progonoma (Stowens, 1957), is even more controversial and some would doubt that it is a true neoplasm. The finding of histologically similar tumours in many parts of the body, such as the epididymis (Frank and

Koten, 1967), shoulder (Lurie and Isaacson, 1961), and mediastinum (Misugi, Okajima, Newton, Kemetz, and de Lorimier, 1965), has effectively silenced the claims of dental or retinal epithelium to be the sole progenitor. Most authorities now agree that this is a tumour of primitive neural crest cells which are capable of differentiating towards melanocytic function and towards neuroblastic structure, both of which are seen in this tumour. The term "melanotic neuroectodermal tumour of infancy" seems the most logical one to use. Electron microscopic appearances (Hayward, Fickling, and Lucas, 1965; Misugi and others, 1965; Neustein, 1967) tend to confirm this view, as does the finding that catecholamines may be formed by the tumour (Borello and Gorlin, 1966). However, the statement that this tumour is derived from primitive neural crest cells seems to beg the question why those cells were present at a given site at that time. If the tumour arises in the maxilla it is perhaps reasonable to infer that they might have had odontogenic potential and that cells in the orbit had been destined for the retina, in which case the present patient might reasonably claim to have suffered from the first recorded true retinal anlage tumour, particularly in view of its structure (Fig. 1). The clinical features and therapeutic approach to neoplasia have been well summarized by Allen, Harrison, and Jahrsdoerfer (1969), and it will be sufficient to say here that local removal is almost always effective and that this entity should probably be regarded as a hamartoma rather than a true neoplasm. In spite of repeated summaries of the world literature, the most recent being that of Borello and Gorlin (1966), it seems that one epidemiological feature of this tumour has been overlooked. In 31 of the recorded cases of its occurrence in the maxilla or mandible in which the race of the patient was stated, only one was a Negro (Williams, 1967), and this case was highly atypical clinically and histologically, whereas out of eleven cases in other parts of the body, seven occurred in Negroes.* There is evidence that other tumours of neural crest origin have a very different distribution and frequency in Ugandan Africans and Caucasians. For example, neuroblastoma occurs less frequently (Davies, 1968). At least 50 per cent. of phaeochromocytomata occur outside the adrenal (Templeton, 1967), and most melanomata occur on the feet (Lewis, 1967). These embryologically linked anomalies appear worthy of further investigation.

Other derivatives of the neural crest include sympathetic ganglia and nerve sheaths. During the course of this survey, a tumour of each of these structures was found to involve the orbit in children under the age of 3 years. Metastasis from adrenal neuroblastoma to the orbit occurs relatively frequently and all such tumours found at this site should be presumed to be secondary deposits until proved otherwise. There is, however, no theoretical reason why the ciliary ganglion should not be the seat of primary neuroblastoma, but this is difficult to prove. Experience with metastatic neuroblastoma in Uganda is limited since, as stated previously, the incidence of adrenal tumours is lower than in Caucasians (Davies, 1968). By contrast, the incidence in Egypt, where Mortada (1967) has accumulated a considerable number of cases, appears to be quite high. When neuroblastoma does occur in Africans, it does not differ functionally, histologically, or clinically from that seen elsewhere in the world. The differential diagnosis from other causes of orbital swelling such as Burkitt's tumour is assisted by the almost invariable presence of infraorbital ecchymoses which regularly accompany neuroblastoma deposits but which are not seen in patients with Burkitt's tumour. Benign tumours of nerve sheaths are relatively easy to diagnose, but their malignant counterparts excite more controversial views, since the distinctive characteristics seen in benign tumours are often absent. Evidence of palisading is usually not found and the diagnosis is based upon the shape of the spindle cells and the relationship both macroscopically and microscopically to nerve sheaths.

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* Present Case 2, and those of Eaton and Ferguson (1956), Lurie and Isaacson (1961), Reyes, Gonzalez-Angulo, and Navarete-Reyna (1964), Frank and Koten (1967), Neustein (1967), and Koudstaal, Oldhoff, Panders, and Hardonk (1968)

Fibrosarcoma displays the same characteristics as in other parts of the body.

The only case of rhabdomyosarcoma seen was of the embryonal variety and did not show cross-striations.

Congenital anomalies seem to show a marked variation in incidence in different parts of the world. In Uganda sacral meningocele is only rarely seen, but nasal myelocele is relatively frequent. It should be noted that, although most of such patients are seen in the first 6 months of life, one child presented with a swelling in the medial side of the orbit at the age of 3 years. In this patient simple excision of the mass of brain tissue appeared curative, and histologically its covering of meninges appeared complete, arguing that connection with the subarachnoid space had been obliterated.

Orbital haemangioma is a common cause of proptosis in most parts of the world and its rarity in this series is puzzling since it is seen elsewhere in the body quite frequently.

Summary

The diagnosis of proptosis due to orbital tumour in a series of sixty cases in Ugandan children is analysed. Nearly half of these cases were due to Burkitt's lymphoma but other conditions seen fairly frequently included chloroma, fibrous dysplasia, and anterior myelocele. Two cases appear to be unique, in that neither aesthesioneuroblastoma nor retinal anlage tumour has been reported previously in the orbit.

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Calculation of total retinal area

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The general topography and the linear measurements of the eye have long been accurately documented, but when, for a recent paper (Taylor, 1970), it was desirable to know the total retinal area, no reference for this was found. A calculation of total retinal area was therefore attempted, using mean linear and radial measurements for the emmetropic eye (Duke-Elder and Wybar, 1961; Thiel, 1955). It is not suggested that the result is exact, but it seems the best available at the present time, using these data.

The following values were assumed in the calculation:

Outer sagittal diameter of globe	24·15 mm.
Inner sagittal diameter of globe	22·12 mm.
Diameter of optic disc	1·50 mm.
Distance of ora serrata from limbus in:	
nasal meridian	6·60 mm.
superior meridian	7·40 mm.
temporal meridian	7·90 mm.
inferior meridian	6·90 mm.
Diameter of cornea:	
vertically	10·60 mm.
horizontally	11·70 mm.

Figs 1 and 2 are schematic representations of the eye, Fig. 1 representing a narrow spherical lune and Fig. 2 a sagittal section through the schematic eye. The letters and angles indicated are used in the text.

Consider the right eye (Fig. 1)

Let PQ be the geometrical axis of the eye. Let O be the centre of the sphere. Let PSQ and PS'Q be two great circles separated by a small angle, $\delta\xi$, and enclosing a narrow spherical lune.

The area of the shaded element of this lune is the product of length and breadth, equal to $\delta x.\ \delta z$. If r is the inner radius of the eye and the small angles are measured in radians, we have:

$$\delta x = r\delta\xi.\ \sin\zeta$$
$$\delta z = r\delta\zeta.$$

Therefore the area of the shaded element is $r^2\delta\xi\ \sin\zeta\ \delta\zeta$.

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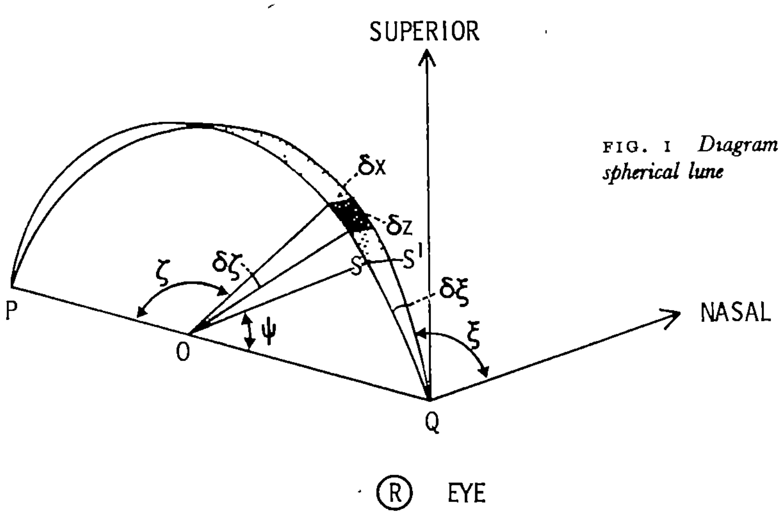

FIG. 1 *Diagram of a narrow spherical lune*

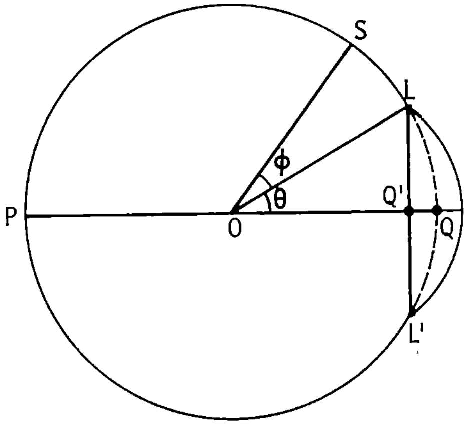

FIG. 2 *Diagram of a sagittal section through the schematic eye*

LL′ = corneal diameter
LQ′ = $\frac{1}{2}$ LL′
OL = R
Sin θ = LQ′/R
θ = $\sin^{-1}$ LQ′/R, the angle whose sine is LQ′/R
LS = ora serrata to limbus
φ = LS/R (radians)

If the retina extends from P posteriorly to SS' anteriorly the retinal area enclosed by this lune is:

$$\int_{0}^{P\hat{O}S} r^2\delta\xi \sin\zeta .\, d\zeta = r^2\delta\xi\,(1 + \cos\psi)$$

Therefore, if we could describe the angle ψ in terms of the angle ξ about the geometrical axis by a function $F(\xi)$ such that $\psi = F(\xi)$, we could calculate the retinal area as:

$$\int_{0}^{2\pi} r^2\,(1 + \cos F(\xi)) .\, d\xi,$$

from which we must subtract the area of the optic disc.

From the data of vertical and horizontal corneal diameters and of the distance of the ora serrata from the limbus in the four main meridians, it is possible to calculate the angle ψ at these meridians. Since the measurements given are external, in these calculations we make use of the outer sagittal radius, here denoted by R, instead of the inner, r. A reasonable assumption has to be made as to the shape of the ora serrata to give values of ψ at intermediate values of ξ which represent parts other than the four main meridians. This assumption is used in place of the expression of ψ as a formal function.

In Fig. 2.

LL' = corneal diameter (known)
LQ' = $\frac{1}{2}$ LL'
OL = R (known)
$\sin\theta$ = LQ'/R
θ = $\sin^{-1} LQ'/R$, the angle whose sine is LQ'/R.
LS = distance of ora serrata from limbus (known)
OL = $OS = R$
φ = LS/R (in radians)

Hence we can calculate $\psi = \theta + \varphi$ at each of the four main meridians. The Table shows the results of these calculations.

Table

Meridian	ξ	$\sin\theta$	θ	ϕ	ψ
Nasal	0	0·4845	0·5058 (28° 59′)	0·5467 (31° 19′)	1·0525 (60° 18′)
Superior	$\pi/2$	0 4389	0·4544 (26° 02′)	0·6128 (35° 07′)	1 0672 (61° 09′)
Temporal	π	0·4845	0·5058 (28° 59′)	0·6543 (70° 29′)	1·1601 (66° 28′)
Inferior	$3\pi/2$	0·4389	0·4544 (26° 02′)	0·5714 (32° 44′)	1·0258 (58° 46′)

It is reasonable to suppose that in each quadrant the angle ψ varies linearly with ξ; that is, we assume that the retinal margin runs smoothly around the eye, the scalloping of the margin being neglected. This assumption implies that in the upper medial quadrant, between the nasal and superior meridians, ψ is given by:

$$\psi = \psi \text{ nasal} + \xi/\tfrac{1}{2}\pi\ (\psi \text{ superior} - \psi \text{ nasal}) \qquad = 1{\cdot}0525 + 0{\cdot}00936\xi$$

If we put $a = 1{\cdot}0525$ and $b = 0{\cdot}00936$, we find the area of the superior nasal quadrant to be:

$$\int_0^{\frac{1}{2}\pi} r^2 \left(1 + \cos\left(a + b\xi\right)\right).\, d\xi$$

$$= \frac{\pi r^2}{2} + r^2 \left[\frac{\sin(a + b\xi)}{b}\right]_0^{\frac{1}{2}\pi}$$

$$= r^2\left(\frac{\pi}{2} + \frac{\sin 1\ 0672 - \sin 1{\cdot}0525}{0{\cdot}00936}\right)$$

$$= r^2\,(1{\cdot}5708 + 0{\cdot}7746) = 286{\cdot}8 \text{ sq.mm.}$$

Similar calculations for the other quadrants give the following results:

Area of superior nasal quadrant	286 8 sq. mm.
Area of superior temporal quadrant	276·8 sq. mm.
Area of inferior temporal quadrant	280·4 sq. mm.
Area of inferior nasal quadrant	289·8 sq. mm.
Total	1133·8 sq. mm.

The disc area remains to be calculated and subtracted. It is given by multiplying the square of the disc radius by π. This amounts to 1·8 sq.mm. The subtraction gives the total area of the retina as 1132 sq.mm.

Obviously the decimal places have been retained only to guard against the accumulation of errors through rounding off.

We suggest that the retinal area be taken as 1100 sq.mm.

We should like to thank Mr. Max Sharratt for verifying the calculus.

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Corneal degeneration in a congenitally diabetic inbred strain of mouse

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Heritable corneal degenerations in experimental animals have been reported infrequently. A few such reports by Loeffler (1932), Douglass and Russell (1947), and Mackensen (1960) might possibly be considered as corneal degenerations but in the last two of these studies the condition was found in mutant mice which were born with their eyelids open, a condition in which corneal damage will develop through exposure. Normally, the eyelids of newborn mice, such as the Swiss Webster strain, do not begin to open until the 12th day. Another instance of corneal degeneration in an inbred line of circling mice (*Mus musculus*) was described by Stein, Norvis, and Mason (1962), but, they provided evidence that the abnormality is more likely to be a secondary reaction to degenerations beginning in the lens during embryonic development.

In humans, corneal dystrophies are inherited degenerations which tend to be bilateral and progressive and have no known aetiology. Since the condition has a genetic origin it would be expected to be most readily found in inbred animals. Many such inbred strains of animal now exist, but no corneal diseases have been reported which can be related to one of the human forms of corneal degeneration or dystrophy. In the present study we report an example of a corneal degeneration in an inbred strain known as KK mice. Our experience with this example leads us to suspect that there may be other types of corneal disease in albino mice which have gone unnoticed because of the poor colour contrast for corneal opacities and the small size of the eye. When such eyes are examined histologically or with an ophthalmoscope or slit lamp *in vivo* the corneal lesions are most readily recognized.

The inbred strain KK was first established by Kondo, Nojawa, Tomita, and Ejaki (1957) in Japan. Spontaneous diabetes mellitus was later discovered in this strain by Nakamura (1962) and confirmed by Tsuchida (1966). Nakamura's examination of 28 KK mice as compared to ten C57B1/6 and five CBA mice showed that most of them yielded glucose tolerance curves similar to those of human diabetics. Control mice gave normal curves. The majority of KK mice showed glycosuria with blood sugar levels exceeding 240 mg./100 ml. Histological findings in KK mice demonstrated degranulation of pancreatic β cells, a deficiency of zinc content in islets, but no detectable change histochemically in insulin content. The livers had higher fat deposition and diminished glycogen content. The adrenals were smaller than normal and the kidneys showed fibrosis. There were reduced thickness of the retina and cataractous changes in two 7-month-old mice. No mention was made of the condition of the cornea; Birnie, Pula, and Hammerle (1967) demonstrated elevated levels of immune reactive insulin in the pancreas in contrast to Nakamura's findings. Treser, Oppermann, Ehrenreich, Lange, Levine, and Camerini-Davalos (1968) demonstrated glomerular lesions in non-obese KK mice similar to those found in humans. Of 39 KK mice 60 per cent. showed early glomerular sclerosis with

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segmental thickening of the capillary walls and basement membranes, frequently associated with exudative nodular lesions. More recently, in our laboratory, Kaczurowski (1970) used a special flat preparation of the retina with silver staining to demonstrate the presence of microaneurysms in the retinal vasculature of KK mice.

In this report we present statistical and histological evidence that a corneal degeneration exists as a hereditary malformation in KK mice beginning very early in life and becoming progressively worse with age.

Materials and methods

KK mice were obtained from the animal colony of the Smith Kline and French Laboratories, Philadelphia. Normal Swiss Webster mice were used as controls. An initial group of 22 KK mice of both sexes was obtained with an age variation of 1 to 7 months. The ages of subsequent acquisitions of over 100 mice were 7 to 24 months. Mice were maintained on a diet of Purina laboratory chow and water *ad libitum*.

Randomly selected mice were examined for evidence of diabetes mellitus by running a glucose tolerance blood sugar curve on blood from the tail vein. All examinations of the eyes were made *in vivo* with a Haag-Streit slit lamp and an ophthalmoscope.

For histology, the mice were killed by the injection of an overdose of Nembutal. The eyes were fixed in 10 per cent. buffered neutral formalin and sections were stained with haematoxylin and eosin for routine staining, von Kossa's stain and alizarin red for calcium deposits, periodic acid Schiff for mucopolysaccharides, and Sudan black for lipids. Special procedures were followed to avoid the extraction of lipids in routine histology.

Results

GENERAL CHARACTERISTICS

KK mice are moderately obese, have ruffled fur (Fig. 1), and are sluggish in their movements.

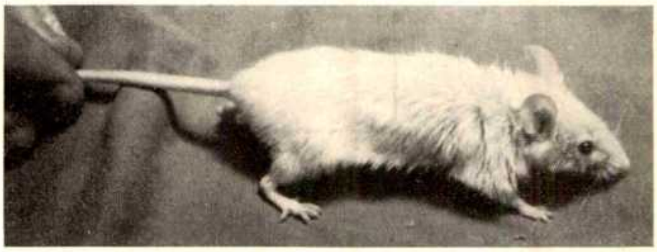


FIG. 1 *KK mouse* (*1 year old*)

They are born with closed eyelids which do not begin to open until the 21st day. Mice with advanced corneal lesions are blind because the opacity is always centrally located. The lesions begin within the first 2 months of life as small opacities less than 0·5 mm. in diameter. With age the opacities extend into the anterior stroma and grow laterally. After 6 months the lesions are bilateral in most cases.

When examined with the ophthalmoscope or slit lamp, these lesions resemble an aggregate of bubble-like cysts forming geometric or irregular geographic map-shaped opacities. They are located in the stroma in the central area, are refractile, and have a metallic or diamond-like lustre (Figs 2 and 3, overleaf). The corneal surface is thicker or elevated in the area of the lesion. Older advanced lesions tend to become vascularized (Fig. 3). When the lesions extend laterally, islands of bubble-like cysts will develop into tiny clusters. The corneal tissue between them is normal, but in time the whole region coalesces into one or more large degenerative areas. Corneal lesions were not found at the periphery.

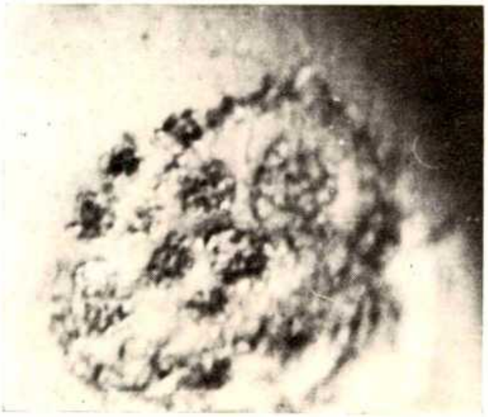


FIG. 2 *As seen through a slit lamp the corneal lesion in a mature KK mouse eye has a large central opacity. The general appearance presents a type of crystalline granularity or bubble-like clusters. The lesion is irregular in shape and uneven in its topography. The corneal periphery shows no detectable pathology. Photographed through a specially modified Haag-Streit slit lamp, Pan X film, 3 sec. exposure at 7·5 volts.* ×170

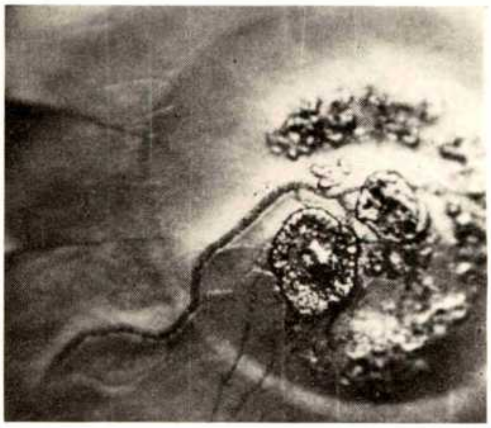


FIG. 3 *Corneal degeneration with neovascularization. The vessels in older lesions extend well into the centre of the lesion. Photographed as in Fig. 2.* ×170

Of the 44 corneae observed in KK mice aged 1 to 7 months which had established diabetic glucose tolerance curves, 41 had central corneal degeneration. None of the twenty corneae in normal Swiss Webster mice had any defect. The incidence of corneal opacities in over 100 KK mice 6 to 18 months old was 75 per cent.

HISTOPATHOLOGICAL EXAMINATION

The lesions begin with swelling of the epithelial cells. In older mice they extend to the anterior and finally into the central stromal region. They then occupy about half of the stromal thickness. The advanced lesions show a separation of the lamellae of the stroma with open or empty spaces. A hyalin-like material is infrequently present between these lamellae in sections stained with haematoxylin and eosin (Figs 4 and 5). No lipid-staining material was found in the lesions. A membrane-like material is present in small segments along the inner surfaces of the empty spaces (Figs 4 and 6).

Histological preparations with alizarin red and von Kossa's stain gave pronounced calcium reactions in the region of corneal degeneration (Fig. 7).

Vascularization of older lesions is present in some eyes (Fig. 4). There is an active but minimal cellular response in these lesions in which polymorphonuclear and mononuclear leucocytes may be seen in small numbers. The epithelium may heal leaving no scar. The posterior stroma, Descemet's membrane, endothelium, and peripheral areas of the cornea were unaffected by the severe central lesions.

Comment

The observations in this preliminary study suggest that an inherited degenerative process exists in the KK mouse cornea. The lesion occurs in a high percentage of randomly selected KK mice, is almost entirely bilateral, and has an early onset. The corneal lesions are light grey opacities. In a pigmented mouse such a defect would be easily visible to the unaided eye because of the strong contrast of the grey opacity against a dark

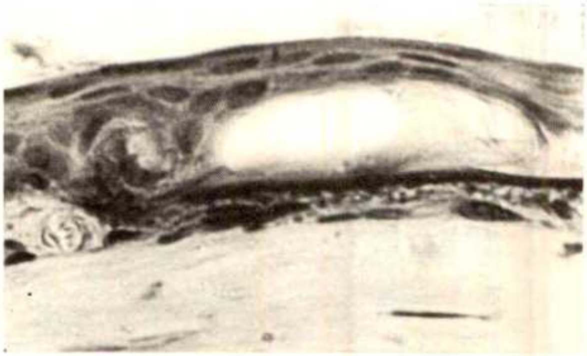
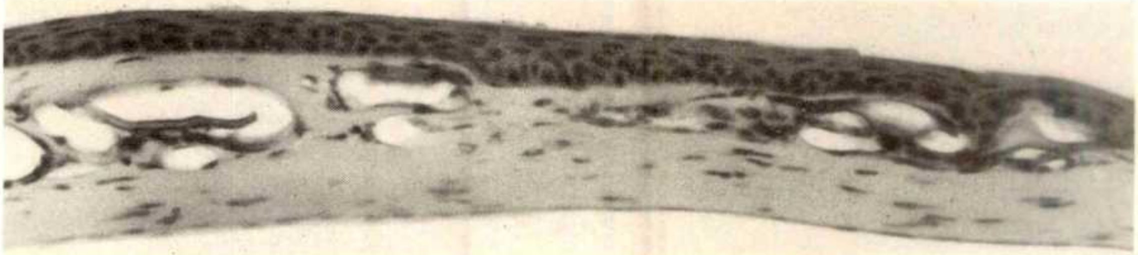


FIG. 4 *KK mouse corneal degeneration. Note large vacuole in disorganized epithelial layer and a membrane-like deposition at its base. Both the epithelial and stromal layers are somewhat thickened. Haematoxylin and eosin.* ×405

(5)



(6)

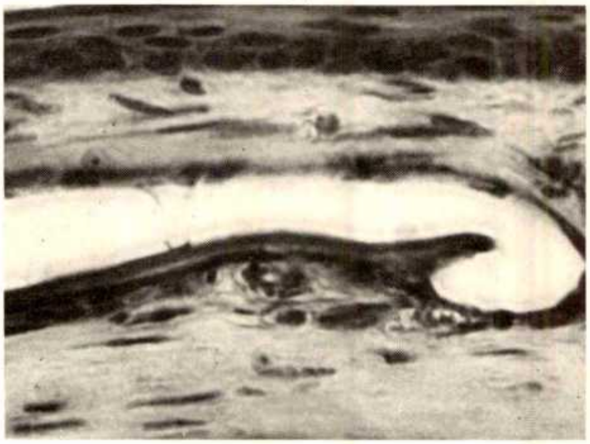


FIG. 5 *KK mouse corneal degeneration. Note multiplicity of vacuoles, located in this instance in the stromal layer. No lipid was detected by histological staining. The vacuoles probably account for the crystalline refraction of light as seen through the slit lamp (cf Figs 2 and 3)*
Haematoxylin and eosin. ×125

FIG. 6 *Large vacuole with a membrane-like deposition on its posterior surface similar to that shown in Fig. 4. There is no great cellular disorganization or infiltration in the epithelium and surrounding stroma. Haematoxylin and eosin.* × 405

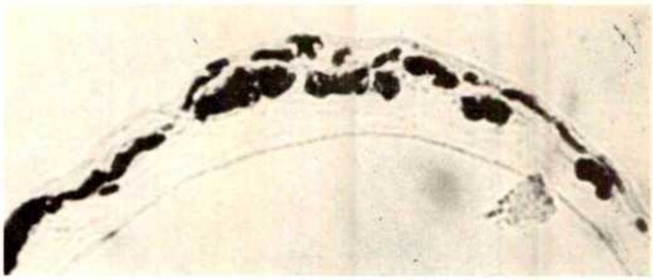


FIG. 7 *KK mouse corneal lesions with massive accumulations of calcium-containing deposits. Calcium was detected in every preparation by alizarin red and the von Kossa stain. Alizarin red stain.* ×94

background. In albino KK mice, the condition is imperceptible on casual observation. This might explain why the many investigators working with KK mice have failed to report the condition for over 13 years. Another possible explanation is that the corneal lesion may be a natural result of the diabetic condition and not of a separate genetic defect. It would then be expected that some mice with less severe diabetes would form fewer corneal defects or mild defects which could be missed even biomicroscopically. In some of the latter groups of animals obtained from the SKF laboratories early in 1969 when their colony was being discontinued, we noted that there was an unusually low incidence of corneal defects. In some groups of KK mice corneal degenerations were found in only 25 per cent. rather than in 90 to 100 per cent. No glucose tolerance curves were obtained on these later mice. It is also possible that accidental cross-breeding with normal mice had occurred.

After this manuscript was completed, a report by Mittl, Galin, Opperman, Camerini-Davalos, and Spiro (1970) described some of the KK mouse corneal abnormalities mentioned above. These investigators gave a good analysis of the prominent extracellular deposition of calcium in the anterior segment of the cornea. They also provided histological evidence that the calcium deposits occurred as carbonate and/or phosphate compounds. When they found that serum calcium and phosphate levels were not elevated in KK mice as compared to normal mice, they suggested that the corneal lesion was not due to hypercalcaemia. The clinical and histological findings in their laboratory and ours are identical. It is interesting that the animals were supplied from the same source—the Smith Kline and French Laboratories.

There is a possibility that these mice may have suffered from a dietary deficiency. This was suggested recently by the work of Hamuro, Shino, and Suzuoki (1970), who found that KK mice developed calcium deposits in the heart muscle when maintained on a stock diet. By manipulating dietary magnesium and phosphorus in purified diets, they were able to augment or completely prevent this tissue calcium deposition. When KK mice were fed diets deficient in magnesium and high in phosphorus, both the heart and kidney were severely affected with high levels of tissue calcium. They found this effect to be associated with a rapid rise in plasma inorganic phosphorus. The same diets did not produce tissue calcification in ICR, C57BL, or CF 1 mice. Ultimately they felt that a diet deficient in magnesium was responsible for the tissue deposition of calcium. No mention was made of the corneal condition but this could easily have been overlooked as mentioned above. If the corneal defect we have observed was caused by a lack of dietary magnesium, then it is possible that a change in the diet could have occurred during the course of our study. This would account for variations in the percentage of ocular defects in subsequent shipments of our own mice. This possibility will be studied.

Certain similarities exist between the KK mouse corneal degeneration and some of the classic descriptions of human corneal dystrophy and corneal degenerations (Duke-Elder, 1965). The KK mouse lesion is primarily a stromal disease which occasionally extends into the epithelium. This is comparable to some of the granular, macular, and crystalline dystrophies. Some features are comparable to the microcystic type of human dystrophy described by Cogan, Donaldson, Kuwabara, and Marshall (1964). The KK mouse disease forms vacuolated cysts as does microcystic dystrophy, but they are most often seen in the corneal stroma. In microcystic dystrophy these cysts are entirely located in the corneal epithelium. There is also some evidence of membrane formation in the mouse cornea. A basement membrane-like structure forms within the corneal epithelial layer in human microcystic dystrophy, whereas in KK mice the laying down of membrane-like material occurs in the lining of the vacuolated cysts in the stroma. In human corneal macular dystrophy the lesions are distributed over the whole cornea. This was not the case in any of the KK mice, in which the lesions were entirely central. In human granular dystrophy, the lesions are located centrally but the tissue between the granular degenerations is normal and clear. In the KK mice there is no granular distribution and the involved area tends to be continuous. In some of the younger animals, however, there are degenerative plaques separated by clear corneal tissue.

The finding of abnormal amounts of calcium in KK mouse corneal lesions provides the first clue to the cause of the tissue damage. The primary questions are:

(1) Is the KK corneal degeneration directly attributable to the diabetic condition?

(2) Is it related or unrelated to the diabetic abnormality through a nutritional deficiency?

(3) Is it a separate genetic disorder?

The KK mouse provides the first experimental model of a heritable corneal degeneration which mimics many of the clinical characteristics of human corneal dystrophies.

Summary

A corneal degeneration has been described in an inbred mouse line, the KK congenitally diabetic strain. The lesion begins in early life, is progressive with age, tends to be bilateral, and is confined mainly to the anterior part of the corneal centre. The lesions appear to be due to an inherited degeneration, but it is not known if they are the result of diabetes or of a separate genetic aberration. The condition is not due to exposure trauma such as that found in mutant mice which are born with slit lids or open eyelids. Histological study has revealed the presence of abundant calcium in the corneal lesions. Recent findings of tissue calcium deposition in the KK mouse heart and kidney after deficient dietary magnesium suggest that the corneal damage demonstrated in this study may also be related to dietary magnesium deficiency and raised dietary phosphorus in diabetic KK mice. The availability of an animal model with one form of corneal degeneration will provide ready access to viable tissues for biochemical and histopathological studies.

The authors are grateful to Dr. James Birnie of Smith Kline and French Laboratories for his advice, assistance, and encouragement in this study. We also wish to thank him and Smith Kline and French Laboratories for supplying us with KK and normal mice and for performing the pharmacological tests on these animals, and Mrs. Addie Wilson for the histological preparations.

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Retinal cysts following cryotherapy

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Cryotherapy, a technique extensively used in retinal surgery during the past few years, is claimed to be a safer procedure than diathermy and photocoagulation (Kirkconnell and Rubin, 1965; Curtin, Fujino, and Norton, 1966; Lincoff and McLean, 1966; McDonald and Tasman, 1967), but occasional complications have been described (Burch and Morse, 1968; Shea, 1968).

The present report records the occurrence of retinal cysts which developed in two patients adjacent to the treated areas shortly after cryotherapy.

Case reports

Case 1, a 27-year-old man, with a recent retinal detachment in the upper temporal quadrant of the right eye, was admitted to the ophthalmology department. The visual acuity of the right eye was 6/7·5, with −4·75 D sph., −0·5 D cyl., axis 30°, and of the left eye 6/6, with −4·5 D sph., −1 D cyl., axis 150°. The right fundus showed a high bullous detachment in the upper temporal quadrant. Two small round peripheral holes and a small horseshoe mid-peripheral hole were seen between 10 and 11 o'clock. All the holes were inside an area of snail tracks and cystoid degeneration. The detached retina flattened after 3 days of rest in bed with a double eye bandage. Thereafter cryotherapy was applied at −50°C in the region of the holes.

After this procedure a marked pale oedematous reaction was noted in the treated areas. Chorioretinal pigmentation, which subsequently increased, was observed 6 days after cryotherapy. On the eleventh postoperative day a flat cyst developed between the 9 and 11 o'clock meridian central to the treated areas, and extended approximately to two disc diameters from the macula (Fig. 1).

Case 2, a 41-year-old woman, underwent a routine fundus examination in the ophthalmology out-patient clinic after refraction. The visual acuity of the right eye was 6/6, with −5 D sph., −0·75 D cyl., axis 180°, and that of the left eye was 6/6 with −5·5 D sph.

The fundus of the right eye showed moderate to severe degenerative cystoid changes and snail tracks in most of the periphery. These changes were particularly marked in the upper temporal quadrant. Small round retinal holes were also present between 10 and 12 o'clock. The left fundus showed similar changes in the periphery of the retina and small round holes were observed between the 1 and 3 o'clock meridians. Transconjunctival cryotherapy was applied in the upper temporal area of both eyes, in the region of the retinal holes. During the application, which was controlled by indirect ophthalmoscopy, a marked reaction was noted, and 7 days later the oedematous treated area showed pigmentation. After a further 7 days a retinal cyst appeared in the upper temporal quadrant of the left eye, between the edges of two previously-treated pigmented areas, extending towards the equatorial zone between the 1 and 2 o'clock meridians (Fig. 2).

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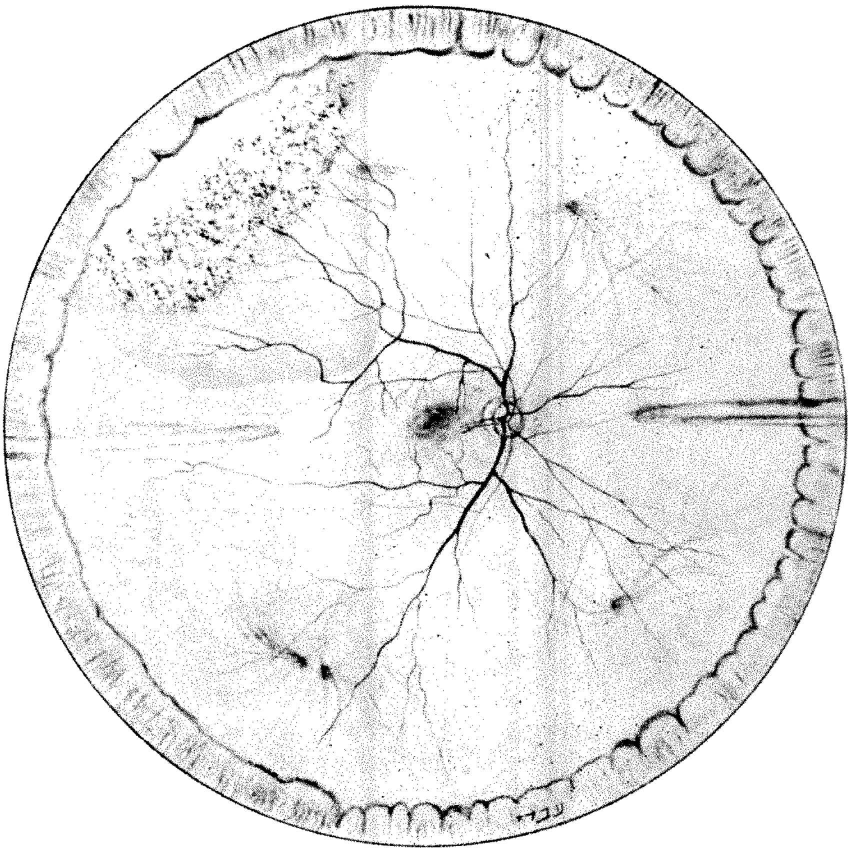

FIG. 1 *Case* 1. *Fundus of right eye* 11 *days after cryotherapy. A flat cyst is present, extending from the edges of the treated area towards the macula*

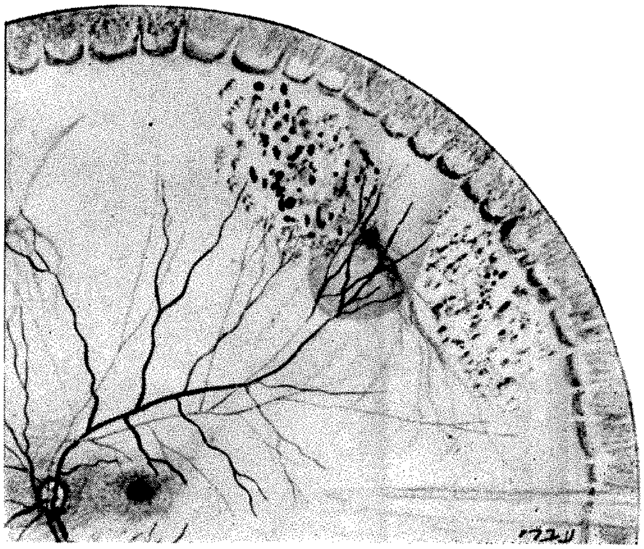

FIG. 2 *Case* 2. *Fundus of left eye* 15 *days after cryotherapy, showing a retinal cyst between the edges of the treated areas and extending towards the equator of the eye*

Discussion

In previous studies occasional complications after cryotherapy have been reported, including uveitis, intrachoroidal haemorrhage, vitreous damage, and haemorrhage and infections following buckling procedures (Kirkconnell and Rubin, 1965; Lincoff and McLean, 1966). It has also been claimed that cryotherapy may produce an extension of a retinal tear and be the cause of retinal split (Shea, 1968). Rhegmatogenous retinal detachment after cyclo-cryotherapy has also been described (Burch and Morse, 1968).

To the best of our knowledge, retinal cysts occurring after cryotherapy have not as yet been recorded. Both cases reported here were young myopic patients who had similar retinal changes before surgery. Both showed areas of cystoid degeneration, snail tracks, and hole formation. The appearance of the cyst may be in some way related to the development of cryotherapy-induced oedema extending from the treated zone to pre-existing areas of degenerate retina.

It is of interest to note that, in both cases, the immediate reaction to cryotherapy was intense. Cyst formation did not appear in similar cases treated with a minimal dose of cryotherapy.

Summary

The development of retinal cysts adjacent to areas treated by cryotherapy is reported in two patients. Both were moderately myopic and showed areas of cystoid changes and snail tracks.

It is possible that cyst formation was due to excessive application of cryotherapy resulting in progressively severe, spreading oedema in previously degenerate retinal areas.

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Adrenogenital syndrome and buphthalmos

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Liverpool

The adrenogenital syndrome is a rare genetic disorder in which there is a failure of one of the enzymes involved in the production of corticosteroids by the adrenal cortex. The condition is an autosomal recessive. Buphthalmos is an uncommon ocular condition, and it would be surprising if buphthalmos and the adrenogenital syndrome were to co-exist in the same patient. This paper describes two such patients.

The synthesis of physiological corticosteroids in the adrenal cortex begins with the hydroxylation of progesterone to form 17-hydroxyprogesterone by the action of 17-hydroxylase. The 17-hydroxyprogesterone is converted to compound S (11 de-oxy 17-hydroxy-corticosterone) by 21-hydroxylase. Finally, the compound S is converted to cortisol by the action of 11-hydroxylase. The most important cause of the adrenogenital syndrome is 21-hydroxylase deficiency, and affected patients present shortly after birth with vomiting and dehydration associated with electrolyte deficiency. As a result of the block in the normal production of the corticosteroids, there is a deficiency of compound S and cortisol, and possibly of aldosterone. Compensatory overproduction of ACTH occurs; as a result there is overproduction of progesterone and its end-product pregnanediol. Excess production of androgens may cause virilization in the female at birth, but in the male child the condition may not be so easily diagnosed by virilization criteria. Treatment, which has to be instituted immediately, consists of the use of corticosteroids of glucocorticoid and mineralocorticoid types. The aim of treatment is to replace the deficient endogenous corticosteroids and suppress the excess ACTH production. The dose of steroids given is monitored by the clinical responses, and by frequent estimation of the serum electrolytes and excretion of urinary 17-hydroxy-ketosteroids, and 17-ketosteroids.

Case reports

Case 1, a male born on February 10, 1964, by breech delivery. The birth weight was 4 lb. 6 oz. He was born of unrelated parents, and was a member of a dizygous pair of twins. The twin sister is also affected with adrenogenital syndrome. There are four other siblings (2 male and 2 female), and one elder brother also has adrenogenital syndrome.

The patient presented with collapse and failure to thrive one week after birth, and was treated with 9-α-fluorocortisone, DOCA, and dexamethasone. On April 4 a moon-faced appearance was noted. A clinical note of prominent eyes was made on June 2. On August 7 he was referred to the Eye Department with an irritable right eye.

Examination

He was examined on August 13 under Pentothal and nitrous oxide anaesthesia, with scoline as muscle relaxant, and positive pressure ventilation. The right eye was described as having buphthalmos, with corneal oedema, deep anterior chamber, and an intraocular pressure of 66 mm. Hg (Schiötz). The corneal diameters were not measured.

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Treatment

Diamox 65 mg. was given four times a day and gutt. pilocarpine 2 per cent. and eserine 0·5 per cent. three times a day to both eyes. On August 16, a right goniotomy was carried out. Later the left eye showed a hazy cornea and on September 9 a left Scheie's operation was carried out. On November 11, the right eye became cloudy; a diagnosis of recurrence of buphthalmos was made and on November 18 a right Scheie's operation was carried out. Thereafter the right cornea remained clear.

Progress

Examination under general anaesthesia on October 10, 1965, showed the ocular tension to be 15 mm. Hg (Schiotz) in both eyes, with cupping of the right optic disc. On March 17 the right corneal diameter was 13·5 mm. and the left 11·5 mm. The ocular tension was 18 mm. Hg (Schiötz) in both eyes, with a cupped right disc.

On August 15, 1966, a right convergent squint was noted, and on May 8, 1968, a right medial rectus recession was carried out. On December 4 the applanation tension was 17 mm.Hg in the right eye and 15 mm.Hg in the left.

On February 28, 1969, when the child was 4 years old, the visual acuity was recorded as 6/60 in the right eye and 6/6 in the left.

Case 2, a male born at term on May 20, 1967, of healthy parents weighed 8 lb. 10 oz. at birth. There is one healthy sibling, but one child died at 10 days of age and the *post mortem* examination showed enlarged adrenal glands.

At 7 days he failed to feed, looked lethargic, and began to lose weight. The serum electrolytes showed potassium 9·8 mEq/litre and sodium 125 mEq/litre. The genitalia were normal. He was treated with hydrocortisone, cortisone, and dexamethasone. The serum potassium fell from 9·8 to 4·8 mEq/litre, and the serum sodium rose from 128 to 134 mEq/litre. The ketosteroid excretion fell from 5 to 1 4 mg./24 hrs, and the 17-hydroxycorticosteroids from 2·9 to 0·8 mg./24 hrs. He was sent home at 2 months of age on dexamethasone 0·5 mg. daily, 9-α-fluorohydrocortisone 0·05 mg. daily, and salt 5 g. daily. A Cushingoid facies was noted at 5 weeks of age. Subsequently, on September 13, 1969, hydrocortisone 10 mg. three times a day was substituted for dexamethasone.

On June 19, 1970, he was referred to the Eye Department with an irritable left eye and buphthalmos was diagnosed. He was treated with Diamox 65 mg. four times a day and gutt. pilocarpine 2 per cent. twice a day to both eyes.

Examination

He was examined under general anaesthesia (using nitrous oxide, scoline and positive pressure ventilation) and hazy corneae and deep cupping of the left optic disc were observed. The applanation tension was 14 mm.Hg in the right eye and 20 mm.Hg in the left. The corneal diameters were 14 mm. right and 15 mm. left. A 24-hr urinary amino acid estimation showed slight generalized amino aciduria.

Progress

On July 8, 1970, the applanation tension was 25 mm.Hg in the right eye and 28 mm.Hg in the left. A left Scheie's operation was then carried out. Examination under general anaesthesia on July 15 showed an intraocular pressure of 38 mm.Hg in the right eye and a right Scheie's operation was carried out on the same day.

Post-operatively the pressure has remained controlled and both blebs are draining. A gonioscopy under general anaesthesia using Worst's lens on September 9, 1970, showed open angles, with patchy depigmentation of the peripheral iris. Vascular arcades were prominent on the anterior iris surface. Schlemm's canal could be seen to be full of blood in the left eye.

Discussion

Buphthalmos may be associated with local ocular abnormalities, such as persistent primary hyperplastic vitreous, Axenfeld's anomaly, and aniridia; alternatively, buphthalmos may be associated with the phakomatoses, such as the Sturge-Weber syndrome, or neurofibromatosis. The only common metabolic disorder associated with buphthalmos is Lowe's syndrome of buphthalmos, amino aciduria, and mental deficiency. It is interesting to note that the second patient showed a generalized slight amino aciduria. Franceschetti (1962), however, found amino aciduria in 46·4 per cent. of 63 cases of buphthalmos. The association of buphthalmos with adrenogenital syndrome does not appear to have been described previously.

The incidence of buphthalmos was stated by Duke-Elder (1969) to be between 0·01–0·04 per cent. of ophthalmic patients. On the other hand Childs, Grumbach, and Van Wyk (1956) found the incidence of adrenogenital syndrome to be 1 in 67,000 live births in the State of Maryland, U.S.A. Buphthalmos and adrenogenital syndrome are therefore rare conditions unlikely to co-exist by chance in the same patient, but as they have been found in two patients in the same area the occurrence is unlikely to be fortuitous. That the association appears not to have been described earlier is due to the fact that, until the advent of systemic steroids and modern biochemistry, patients with congenital adrenogenital syndrome died shortly after birth, before the onset of buphthalmos could be observed.

Two possibilities occur: that the relationship between buphthalmos and adrenogenital syndrome is genetic, or that the occurrence of buphthalmos in cases of adrenogenital syndrome is due to treatment with systemic steroids.

The latter theory, that the buphthalmos is due to the administration of systemic steroids, is at first sight attractive. However, most authors agree that the rise in intraocular pressure is much less marked after treatment with systemic steroids than after the use of local steroids. Williamson, Paterson, McGavin, Jasani, Boyle, and Doig (1969) examined 148 patients with rheumatoid arthritis who were treated with systemic steroids and found only one case of steroid glaucoma. Bernstein and Schwartz (1962), after examining 48 patients receiving long-term steroid therapy, concluded that there was a small but statistically significant increase in intraocular pressure. Buphthalmos does not appear to have been described earlier with systemic steroid treatment, but Hofmann and Hauser (1964) described a case of juvenile glaucoma in a 10-year-old boy who was given systemic steroids for lupus erythematosus. Duke-Elder (1969) goes so far as to suggest that, if glaucoma occurs with local steroid therapy, systemic therapy may be substituted for local therapy.

It seems, therefore, that there is probably a genetic relationship between buphthalmos and adrenogenital syndrome, especially as the former, like the latter, is frequently inherited by means of a recessive gene. Patients with adrenogenital syndrome do not show other genetically related defects, apart from abnormalities of the urogenital tract.

From a practical point of view it is of little consequence whether the buphthalmos is due to steroid overdosage or to a genetic abnormality; in both cases the dose of steroid given should be as low as is compatible with the child's health and vitality. All who have the responsibility for looking after cases of adrenogenital syndrome should be aware of buphthalmos as a possible complication.

Summary

Two instances of buphthalmos occurring in cases of adrenogenital syndrome are described. It is suggested that these conditions are associated, and that the association is probably genetic.

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Experimental asteroid hyalopathy

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The presence of asteroid bodies in the vitreous, designated asteroid hyalopathy by Rodman, Johnson, and Zimmerman (1961), is an interesting but rare condition of obscure aetiology. In spite of the presence of these vitreous opacities, there is hardly any deterioration in the acuity of vision, hence the paucity of available pathological material for study and analysis.

Many diseases have been observed to be associated with asteroid bodies from time to time, but no causal relationship has been demonstrated. A possible association with diabetes mellitus and hypercholesterolaemia has been suggested (Smith, 1958, 1965; Hatfield, Gastineau, and Rucker, 1962; Agarwal, Mohan, Khosla, and Gupta, 1963; Bard, 1964). In our series of cases, the occurrence of asteroid bodies in association with hypercholesterolaemia appeared equivocal, but the presence of vascular changes due to associated diabetes and hypertension has been recorded in many patients (Lamba and Shukla, 1970).

The aim of the present investigation was the experimental stimulation of the production of asteroid bodies in the vitreous humour by induced hypercholesterolaemia, and by local alterations in the state of the vitreous.

Materials and methods

(1) *Experimental hypercholesterolaemia*

This was produced in two groups of seven healthy albino rabbits weighing between 1·5 and 2·5 kg. All the animals were given 1 g. cholesterol (Merck) and 5 ml. olive oil daily with the standard diet for 4 to 16 weeks. The control animals received only the standard diet. Fortnightly estimations of blood cholesterol levels were carried out. When the animals were killed, the eyes were fixed in 10 per cent. formalin, and examined by paraffin and frozen sections for lipid material. The stains used were haematoxylin and eosin, Sudan III, and osmic acid.

To observe the results of mild aseptic inflammation in association with hypercholesterolaemia, a mild sterile chorioretinitis was produced by scleral diathermy in the second group of seven rabbits.

(2) *Intravitreal injection of hyaluronidase*

Twelve guinea-pigs were anaesthetized by the open ether method, and anethaine drops were instilled into the conjunctival sac. After the eye had been fixed with forceps, a 26-gauge needle on a tuberculin syringe containing 75 i.u. hyaluronidase* in 0·1 ml. of a solution of physiological saline was carefully inserted into the vitreous through the pars plana. The enzyme was injected slowly into the middle of the vitreous and the needle was prevented from touching any part of the retinal surface. When this was done properly no bleeding was seen to occur intraocularly or on the surface. The needle was then withdrawn and the animal returned to its cage. These animals were observed with the slit lamp and by ophthalmoscopy for up to 8 weeks, after which they were killed and the vitreous was aspirated and examined microscopically.

The fellow eye was treated in exactly the same manner by injecting physiological saline only, as a control.

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*Hyaluronidase BP (Ovine) Tata Fison Industries Ltd.

Observations

HYPERCHOLESTEROLAEMIA IN RABBITS

The average normal serum cholesterol level in the rabbit was 40–60 mg. per cent. In general the serum cholesterol levels showed a steady increase varying directly with the duration of cholesterol feeding, but there was considerable variation in the total blood cholesterol level, ranging from 464 to 2,040 mg. per cent., after 4 to 6 weeks of feeding. With this amount of cholesterol circulating in the blood, obvious fatty lesions could be seen in the eyes and these were proved microscopically.

The changes observed in the various ocular tissues are given below.

Cornea

There was haziness in the peripheral part with superficial vascularization. The corneal opacification occurred at the level of the superficial stroma and extended across only half the circumference. Microscopical examination showed subepithelial sudanophilia with vascularization from the limbus. The corneal thickness was normal.

Iris

Extensive lesions were common. The typical iris plaque began as white dots or flakes which enlarged and coalesced to form dense white areas. Microscopically the earliest change was the appearance of lipid-filled macrophages or foam cells. As the lesion enlarged a characteristic fatty plaque was formed under the posterior epithelium. Occasionally the plaque projected backwards into the posterior chamber covered by iris epithelium (Fig. 1).

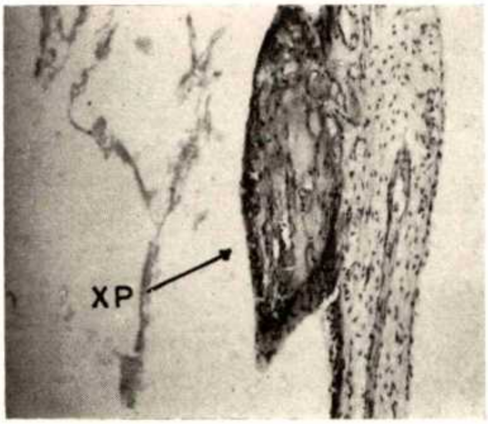

FIG. 1 *Xanthomatous plaque in posterior surface of iris with dim outline of foamy cells. Haematoxylin and eosin.* × 100

Ciliary body

Deposits were seen here in all animals, this being the first ocular change. The droplets of lipid and foam cells were located mainly in the anterior parts of the ciliary body and in the ciliary processes. Their origin showed myxoedematous changes as a reaction to the deposition of lipid.

Vitreous and retina

Fundus examination of the cholesterol-fed animals showed no significant alteration from the normal retina apart from a slight indistinctness of the retinal vessels. The vitreous

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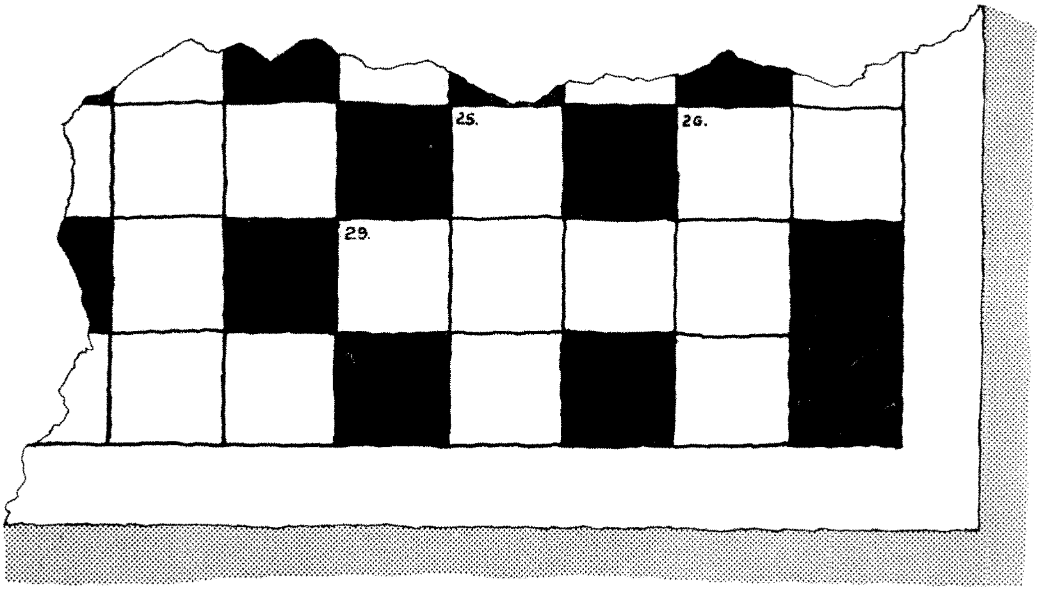

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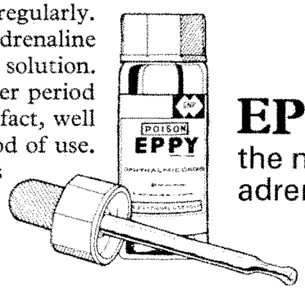

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humour remained clear with no particles or bodies akin to asteroid hyalitis. Microscopical examination failed to demonstrate sudanophilia in the retinal layers, at the optic nerve head, or in the vitreous.

Diathermy to the sclera over the region of the equator was carried out to find out whether hypercholesterolaemia combined with sterile mild inflammation could induce the appearance of vitreous bodies. Ophthalmoscopy showed evidence of reaction in the choroid or retina but no bodies appeared in the vitreous.

HYALURONIDASE INJECTION IN GUINEA-PIGS

In ten guinea-pig eyes, the media became hazy after intravitreal injection of the enzyme. A few cells with plasmoid aqueous were seen in the anterior chamber within 2 to 4 hours. Vitreous liquefaction was observed 24 to 48 hours after injection, and was confined to the area injected. After about 4 days, bright, angular, discrete, refractile particles (probably asteroid bodies) were visible in the anterior part of the vitreous. The particles were static as seen with the slit lamp. The retina appeared to be normal, without holes or detachments. Posterior polar cataract developed in one animal after 7 to 8 weeks.

When examined with polarized light under the microscope, the particles exhibited birefringence of the large inner zone and a thin isotropic peripheral layer of condensed vitreous filaments (Fig. 2A and B). The particles stained intensely with a metachromatic stain, such as Alcian blue. Histopathologically the ocular coats were normal except for scanty infiltration by the inflammatory cells.

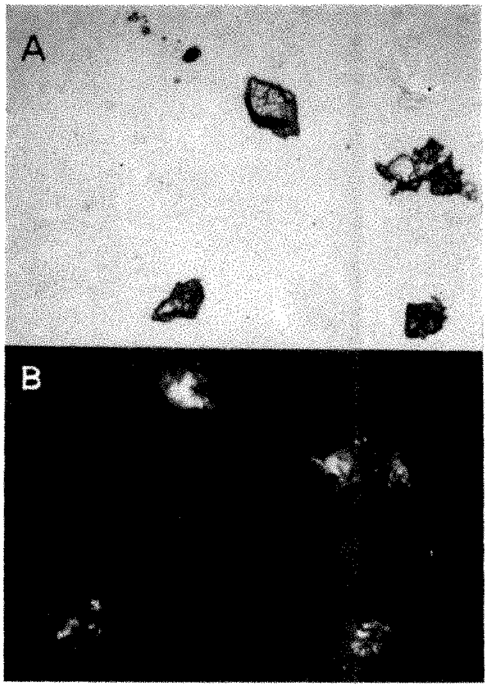

FIG. 2A *Vitreous bodies as seen under the microscope by ordinary light.* × 72

B *Same field photographed with polarized light, showing birefringence of inner zone of particles.* × 72

The animals were followed up clinically, and the vitreous humour was seen to begin to clear, reaching a steady state after 6 weeks when the refractile particles became few and fine.

Discussion

Experimental production of asteroid bodies may be discussed under the following heads:

(A) Hypercholesterolaemia alone as an aetiological factor.

(B) Hypercholesterolaemia associated with mild aseptic ocular inflammation.

(C) Altered mucopolysaccharide metabolism of the vitreous.

(A) HYPERCHOLESTEROLAEMIA

There seems to be no direct correlation between the severity of the lesions induced in the eyes and the raised serum cholesterol levels. The length of time during which cholesterol is fed to rabbits or hypercholesterolaemia is maintained determines the amount of deposition of fat. Such an experimental model is more akin to the atherosclerosis of old age than to acute loading of the body fluids with increased lipid.

There seems to be unanimity among workers in their observations on the disposition of fatty material in the limbal area of the cornea, iris, and ciliary body after cholesterol feeding (Cogan and Kuwabara, 1959; Janes, 1964). Our findings agree with theirs. There is lack of agreement, however, concerning the deposition of fat in the retina. In our experiments and in those of Cogan and Kuwabara (1959), no sudanophilia was observed in the retina, but Janes (1964) found increased sudanophilia in the myelin of the optic nerve and nerve-fibre layer of the retina and also in the rods and cones.

The vitreous humour remained clear throughout with no appearance of particles or bodies akin to those of asteroid hyalitis, as in the previous studies of Cogan and Kuwabara (1959) and Janes (1964). Biochemical investigations in series of cases of asteroid hyalitis led Smith (1958), Agarwal and others (1963), and Bard (1964) to think that hypercholesterolaemia was a probable aetiological factor. Since the present experimental series did not demonstrate the deposition of such particles or the presence of such bodies in the vitreous, it is reasonable to suppose that hypercholesterolaemia *per se* is not the principal factor in the development of asteroid bodies. However, Rosen (1952) observed asteroid bodies in cases of primary hypercholesterolaemia.

(B) HYPERCHOLESTEROLAEMIA WITH OCULAR INFLAMMATION

Because the asteroid bodies have often been reported to be unilateral and occasionally to be associated with choroiditis, a mild aseptic ocular inflammation was produced in the experimental animals. The results differed little from those in the first group, and the intraocular inflammation did not seem to contribute to the production of asteroid bodies.

(C) ALTERED MUCOPOLYSACCHARIDE METABOLISM OF THE VITREOUS BODY

The origin of these calcium-containing lipids is uncertain. Pau (1965) thought they originated from the pigmentary epithelial cells. Considering that hyaluronic acid deficiency may assist in the precipitation of the particles (calcium ions and lipid) present in normal vitreous (Lamba and Rajan, 1970), an intravitreal injection of hyaluronidase was given to a group of animals. This injection removed the hyaluronic acid from the vitreous by upsetting the delicate balance and resulted in the precipitation of particles of a calcium-lipid complex. (The viscous polymerized hyaluronic acid is re-formed about 6 weeks after hyaluronidase injection *in vivo*.) The particles observed in the present experiments showed clinical features simulating asteroid bodies. Microscopically the particles conformed to the recently described histochemical features of vitreous bodies seen in cases of asteroid hyalitis (Rodman, Johnson, and Zimmerman, 1961). When examined under the polarized light they appeared to be composed of fine birefringent material. They stained metachromatically with Alcian blue. The appearance of bright refractile particles in the vitreous after the injection of hyaluronidase was also observed by Pirie (1949), but their nature was not investigated.

Summary

Experiments were carried out to ascertain whether the ingestion of cholesterol by animals could produce visible vitreous bodies (asteroid hyalitis). On the basis of our investigations and the reports of earlier workers, it may be supposed that hypercholesterolaemia *per se* is not the principal factor in the development of asteroid bodies. Local causes may result in the precipitation of macroscopically visible particles of calcium and cholesterol (normal constituents of vitreous). To investigate the role of local changes in the vitreous, hyaluronidase enzyme was injected into the vitreous humour; this produced white, angular, discrete particles which were clinically and microscopically similar to those seen in asteroid hyalopathy.

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Binocular Amsler's charts

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Amsler's charts have long proved to be very useful for detecting organic macular and paramacular disorders. The chart consists of a grid of lines with a central fixation dot, the whole chart at 30 cm. distance subtending an angle of 20° (Amsler, 1949).

In the examination of functional amblyopia, we have found that the use of an Amsler chart can be very helpful in understanding the difference between anisometropic amblyopia and the amblyopia of microtropia. In amblyopia ex anisometropia a central scotoma is almost always indicated by the patient, whereas in microtropic amblyopia with central fixation the scotoma is as a rule paracentral and on the temporal side. The Amsler chart with red lines has proved to be more sensitive than that with white ones. The patient must always be asked to compare the amblyopic eye with the good eye.

The functional scotomata are of course not as clearly described as organic scotomata. The lines are not usually completely extinguished in certain areas, but become intermittently hazy. Attention must be paid to the fact that fixation should not be shifted away from the central spot.

To extend this uniocular examination into a binocular examination, we have used Amsler's charts with polarized projection. A slide with a complete Amsler's chart is seen with the amblyopic eye, whereas only the outer lines and the fixation dot are seen with the normal eye. With binocular vision, the scotomata are larger and more discernible. In amblyopia ex anisometropia a central scotoma is again found (Fig. 1). In severe microtropic amblyopia, the Amsler's chart is suppressed. In slight microtropic amblyopia with central fixation, the scotoma is again found to be on the temporal side, but with binocular vision it extends over the middle, the nasal side being usually unaffected (Fig. 2). This is understood to be a fixation point scotoma, not a central scotoma.

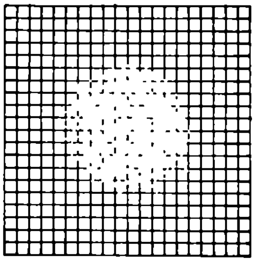

FIG. 1 *Central scotoma in anisometropic amblyopia*

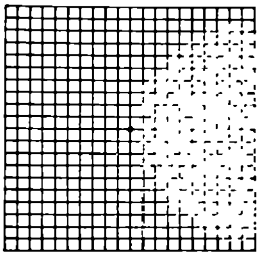

FIG. 2 *Paracentral scotoma in right microtropic amblyopia*

The same results are obtained with Amsler's charts used on the synoptophore. Here again, a complete Amsler's chart is put before the amblyopic eye whereas only the outer

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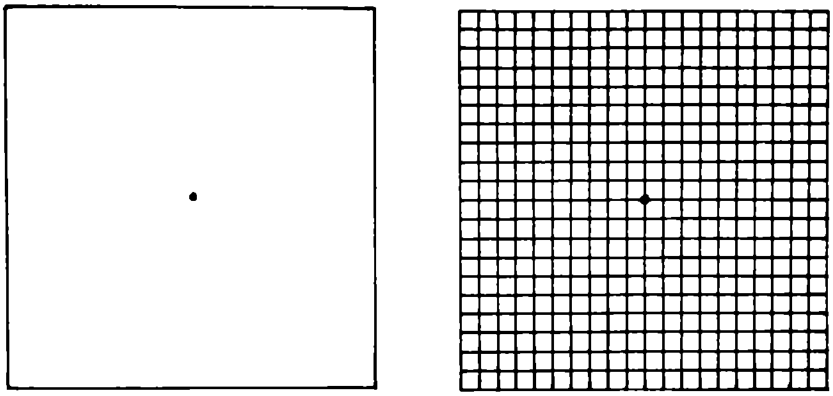

FIG. 3 *Slides for binocular Amsler's chart*

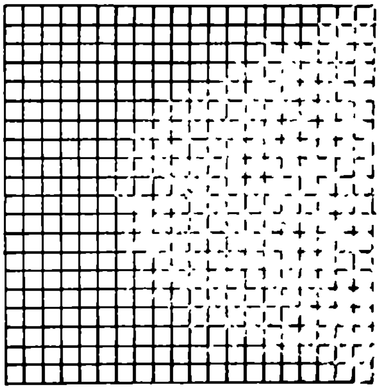

FIG. 4 *Scotoma of right microtropia in binocular vision*

lines and the fixation dot are seen by the normal eye (Fig. 3). For the synoptophore, the charts have to be reduced in size, subtending an angle of only 10° instead of 20°. The use of these binocular charts on the synoptophore has become part of the routine examination in our practice in these cases. It proves especially informative when the gap in the light streak with striated lenses is not seen. By this simple means a rapid diagnosis of suppression areas can be made and central, paracentral, and fixation point scotomata can be differentiated (Fig. 4).

Summary

Binocular Amsler's charts are proposed for detecting functional scotomata in binocular vision.

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Tonometer Testing Station

To the Editorial Committee of the **British Journal of Ophthalmology**

SIRS, A station for the testing of tonometers run by the Ross Foundation with the support of the Faculty of Ophthalmologists has functioned in Edinburgh for almost 20 years. Owing to the increasing use of applanation tonometry and the fact that the methods of inspection and standardization of Schiötz tonometers are now well established and generally accepted, it is proposed to close the Edinburgh Tonometer Testing Station which was originally established on a research basis. The publication of this letter will, I think, help more than anything else to explain the position to the members of the profession.

Yours faithfully,
C. R. S. JACKSON

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Book reviews

Stereoscopic Manual of the Ocular Fundus in Local and Systemic Disease. Vol. 2. By F. C. BLODI, L. ALLEN, and O. FRAZIER. 1970. Pp. 135 + ix, 112 pairs of stereo transparencies with viewer, 53 figs. Mosby, St. Louis; Kimpton, London. (£17·75)

Although ophthalmologists are well aware of the advantages of stereoscopic vision, many are content with uniocular views and illustrations of the fundus. This superb production should help to convince them that the extra time, trouble, and expense required for stereoscopic fundus photography are well worth while. The sixteen reels, each containing stereo-photographs in colour of seven fundus conditions, can be viewed with the folding viewer supplied and provide impressive illustrations of the normal fundus, congenital anomalies, degenerative changes, diseases of the optic nerve and macula, retinopathies associated with systemic disease, and inflammatory, neoplastic, and traumatic conditions. The photographic techniques used are described in detail and there is a useful chapter on the interpretation of fluorescein angiograms.

The main text contains clinical details of the patients whose fundi are illustrated in the photographs, and makes more interesting reading than a conventional textbook description. In many cases fluorescein angiograms are included with the text and demonstrate the additional features of diagnostic importance that can be derived from this technique.

The high price of this manual will preclude many students from buying it, but it should certainly be available wherever ophthalmology is taught, and a thorough study of the photographs will make an excellent introduction to the study of fundus abnormalities.

Famous Hungarian Ophthalmologists. Edited by MAGDA RADNÓT and compiled by I. GYÖRFFY. 1970. Pp. 31, 12 figs. Akadémiai Kiadó, Budapest.

The fact that the next Congress of the European Ophthalmological Society is to be held in Budapest has led Magda Radnót, the president-elect of the Congress, to edit a brochure giving the life-story of twelve of the most famous Hungarian ophthalmologists who were associated with the Medical Faculty of the University of Budapest, which incidentally celebrated its 200th anniversary in 1969. The series starts with János T. Fabini, who was appointed to one of the first chairs of ophthalmology in Europe in 1817 and wrote in Latin an early Hungarian textbook of ophthalmology, a book translated into several languages and widely used in Italy and Holland. It ends with such household names as those of Blaskovics and Imre, whose advances in ophthalmic plastic surgery are to be found in textbooks all over the world. The series of twelve short biographies, each illustrated with a portrait, forms a delightful introduction to the forthcoming Congress.

So You Have Cataracts. What You and Your Family Should Know. By A. E. SLOANE. 1970. Pp. 98, 5 figs. Thomas, Springfield, Ill. ($5.75)

The improved education of the public about medical conditions promotes the need for information for patients who have cataracts. This book does much to explain the nature of cataracts and their treatment, and treats the details of post-operative management by answering rhetorical questions. As it is written in large print, the style is reassuring for the patient, and fears caused by common superstitions are allayed. The author himself adheres to the accepted modern concepts of cataract surgery. When the subject under discussion is controversial, such as the use of intraocular implants, the author cautiously refers the patient to his own doctor and maintains his style of reassurance throughout the text. The book is well written and can be highly recommended to patients who wish to know the reasons for their surgeons' decisions in the treatment of cataracts.

Ocular Examination. Basis and Technique. By A. H. KEENEY. 1970. Pp. 272, 161 figs, bibl. Mosby, St. Louis (Kimpton, London). (£6·85)

This is an excellent review of current ophthalmic diagnostic techniques. It does not aim to describe and evaluate every authors' preference of many techniques. Bacteriology and radiology are excluded, but the specialist procedures of fluorescein angiography, ultrasonography, and electrophysiology are discussed and kept in perspective. The whole book is pervaded with a practical clinical approach which is both refreshing and stimulating. Useful clinical tips and observations abound, making the book invaluable for both the beginner and the experienced ophthalmologist. With such an individual approach there are many minor points that could be contested or even opposed, but this enhances rather than detracts from the value of the book.

It may seem odd to have the first chapter on the organization of the private office. This may well be of importance to the American internist about to embark on his private career, but it will be of little interest to the impoverished English registrar.

Notes

European Contact Lens Society of Ophthalmologists

I Scientific Congress, June, 1971

The I Scientific Congress of the European Contact Lens Society will be held at the Royal College of Surgeons of England, London, on June 2–4, 1971. The subjects for discussion will include keratoprosthetics. The registration fee, which includes luncheons, reception, and the congress banquet at the Royal College of Surgeons, will be:

Members of the European and American Contact Lens Society:	£12	($30)
Non-members:	£20	($50)
Ophthalmologists in training:	£10	($25)

(Non-medical personnel may apply if sponsored by an ophthalmologist).

Application should be made to the Congress Secretary, Moorfields Eye Hospital, High Holborn, London, W.C.1., England.

International Symposium on Geriatric Ophthalmology

Saint-Vincent (Valle d'Aosta), Italy, May 30 to June 1, 1971

This international symposium will be held under the patronage of the Società Oftalmologica Italiana. Many authoritative speakers have announced their desire to participate and they will be dealing with the physiopathological and clinical aspects of the senile eye.

Those interested should write to the Secretary: Dott. B. Bellan, Ospedale Oftalmico di Torino, Via Juvarra 19 – 10122 Torino, Italy.

Jerusalem Seminar on the Prevention of Blindness

August 25–27, 1971

A seminar on the prevention of blindness will be held in Jerusalem from August 25 to 27, 1971, under the auspices of the Israel Academy of Science and the Humanities. The meeting will discuss measures used for the prevention of blindness in developing and developed countries. More particularly, an attempt will be made to assess the comparative effectiveness and cost of these measures.

The following subjects have been chosen for discussion: keratomalacia, amblyopia, glaucoma, diabetic retinopathy, retinal detachment, cataract, and corneal opacification. The last two subjects will be discussed with special reference to developing countries, and will include trachoma, onchocerciasis, malnutrition, virus diseases, and village medicine.

Those interested should write to Prof. I. C. Michaelson, Hadassah University Hospital, P.O. Box 499, Jerusalem, Israel.

International Society of Geographical Ophthalmology

II Conference, Jerusalem, August 23 and 24, 1971

Immediately preceding the above seminar, on August 23 and 24, the second Conference of the International Society of Geographical Ophthalmology will take place. Various aspects of ophthalmic diseases as they appear in various parts of the world will be discussed. Particular reference will be made to the conditions and their incidence which are to be considered in the seminar dealing with the prevention of blindness.

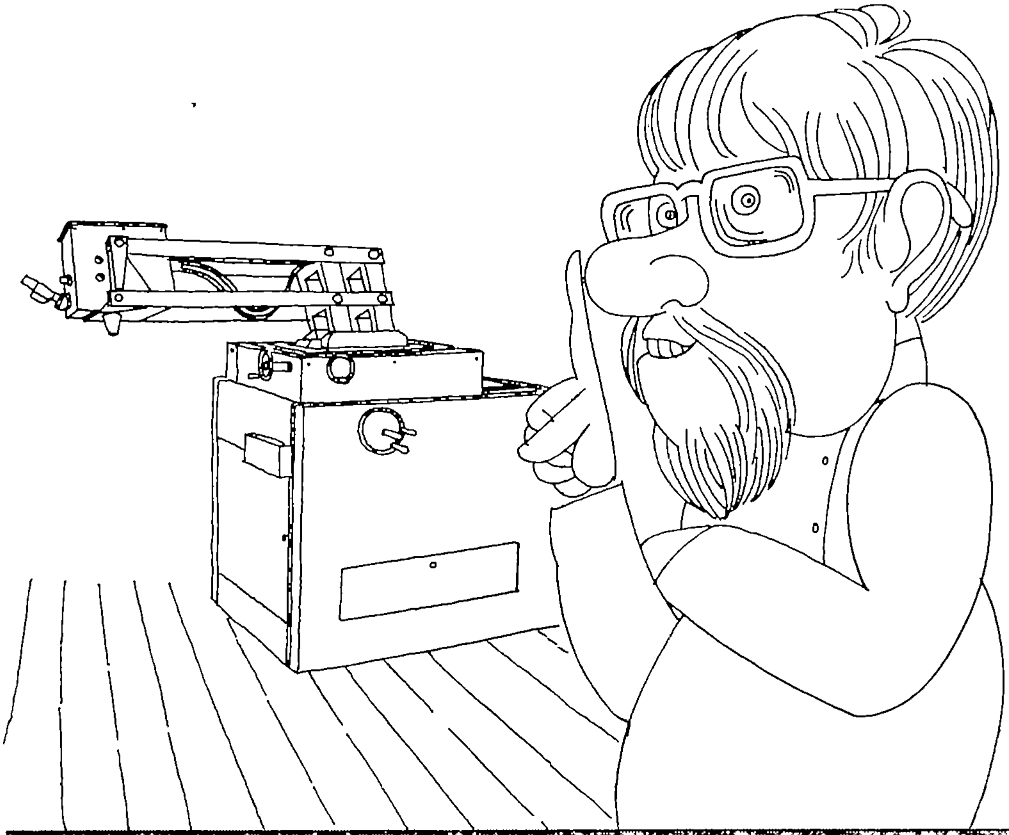
Those interested should write to Dr. E. Cass, Box 24, Fort Smith, N.W.T. 15, Canada.

Corrigenda

In the paper by J. Graham Scott and J. E. Kerrich entitled "Live trachoma vaccine and topical therapy", which appeared in the March issue (*Brit. J. Ophthal.* (1971), 55, 189), please make the following corrections:

p. 189, l 17, *for* 113 *read* 133
 l 2 from bottom, *for* 552 *read* 553
p 190, l. 12, *for* Table II *read* Table I
p. 191, l. 3, *add*. In the Figure, the digits beside each point denote the numbers of observations.

It is regretted that the authors' proof corrections were delayed by the Post Office strike.



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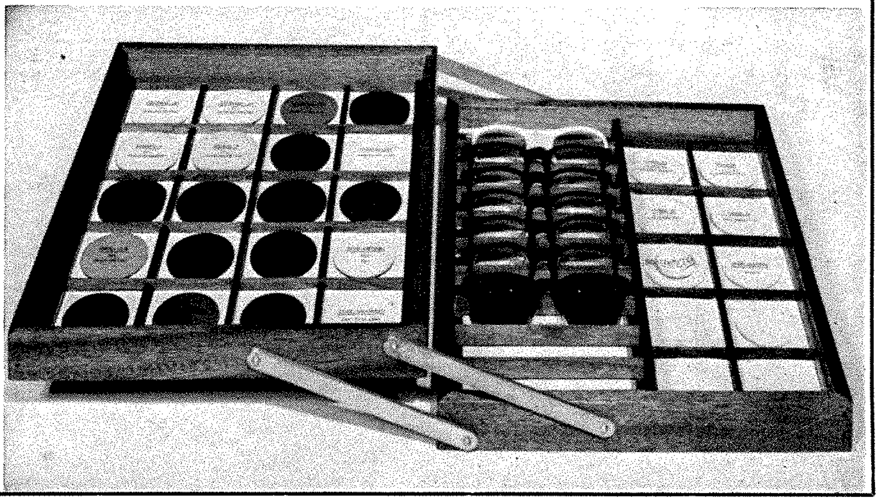

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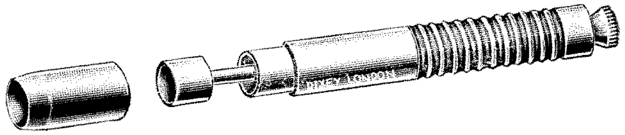

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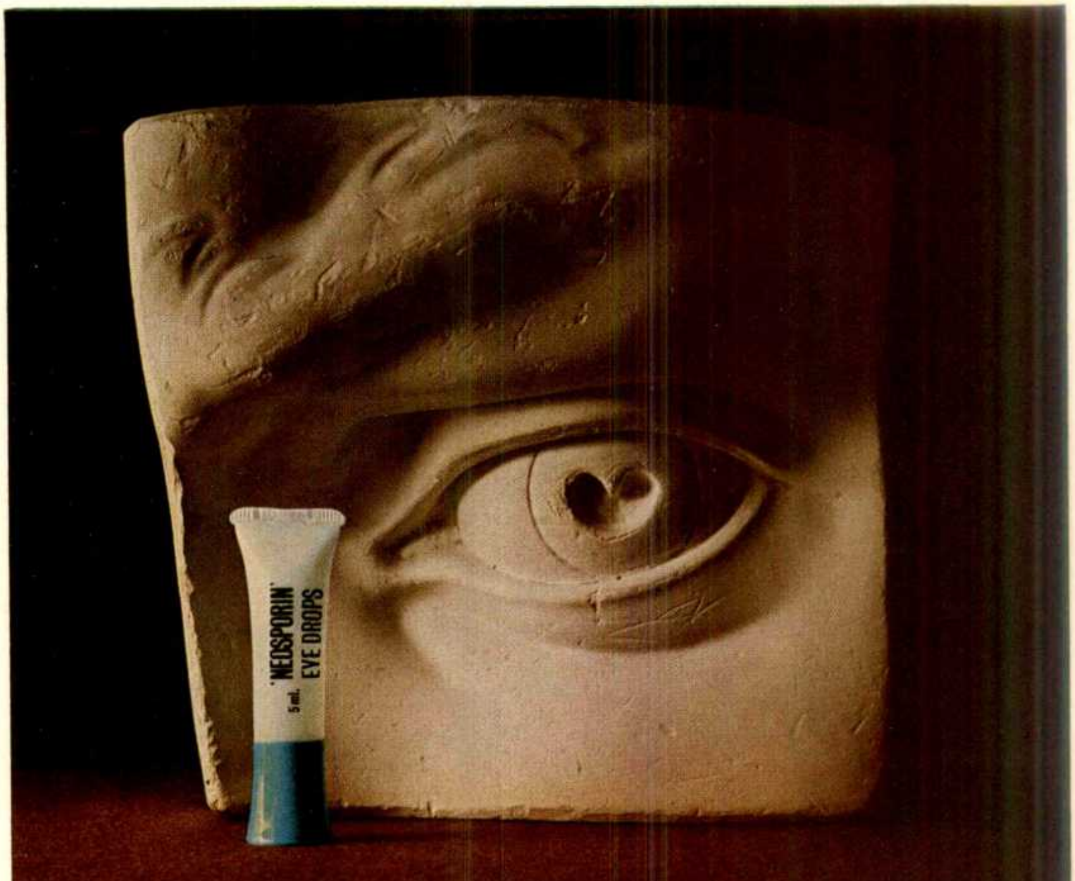

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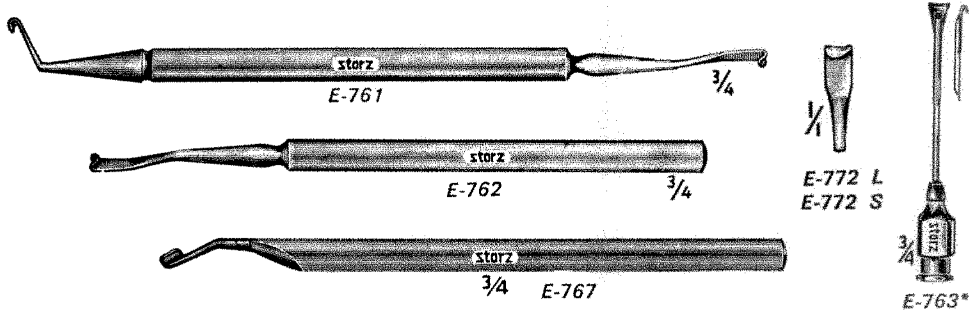

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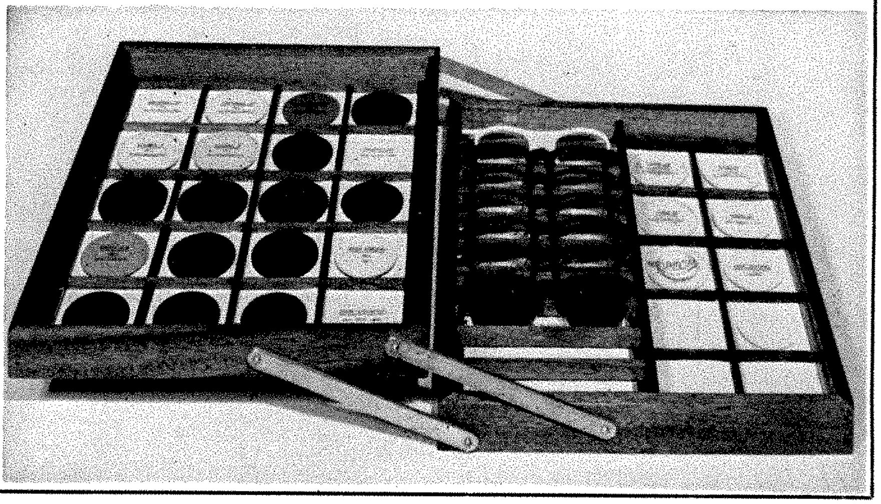

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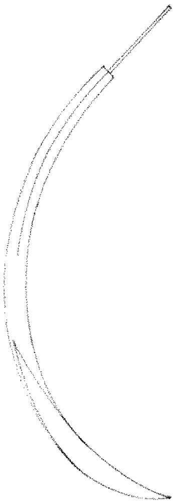

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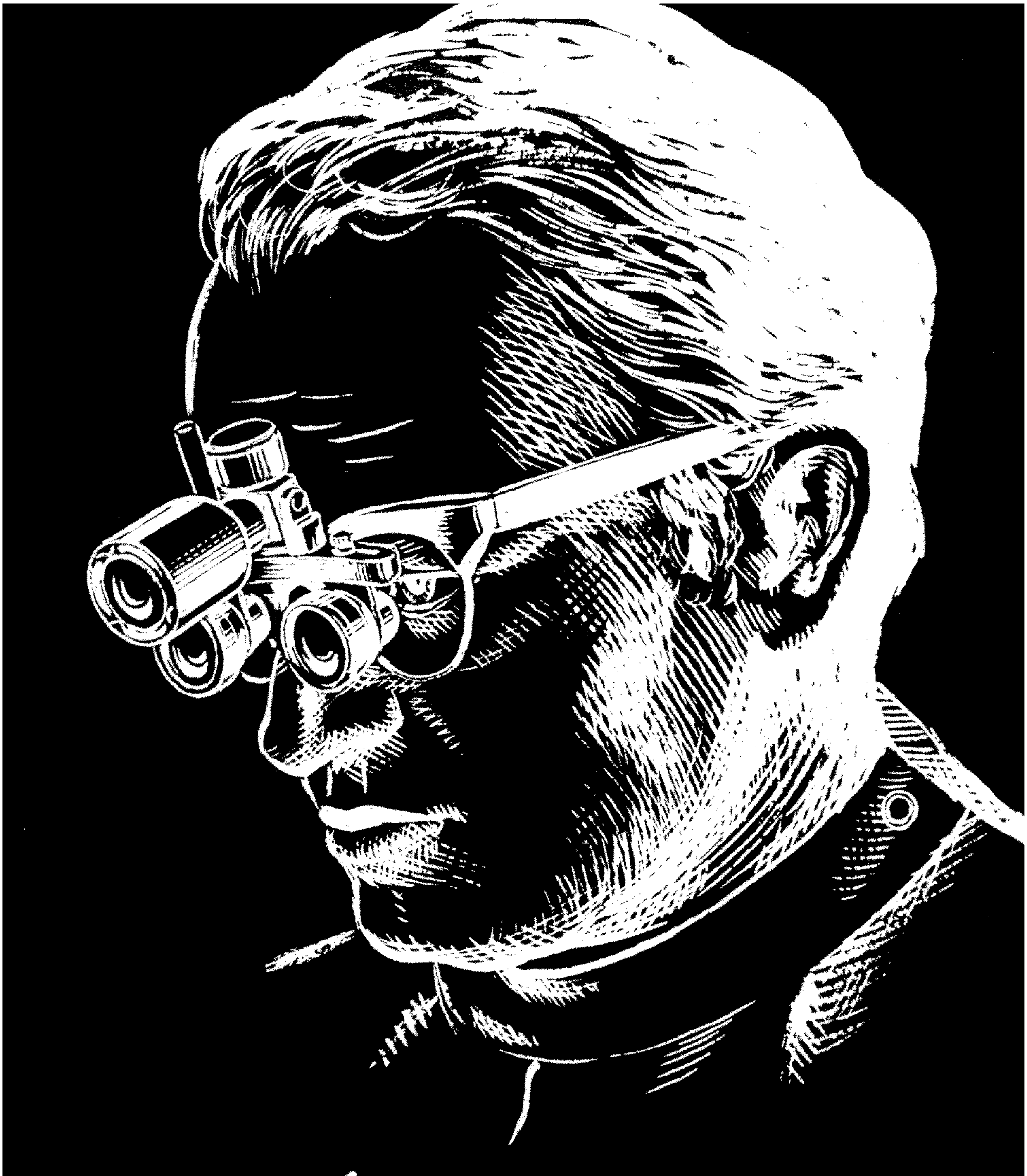

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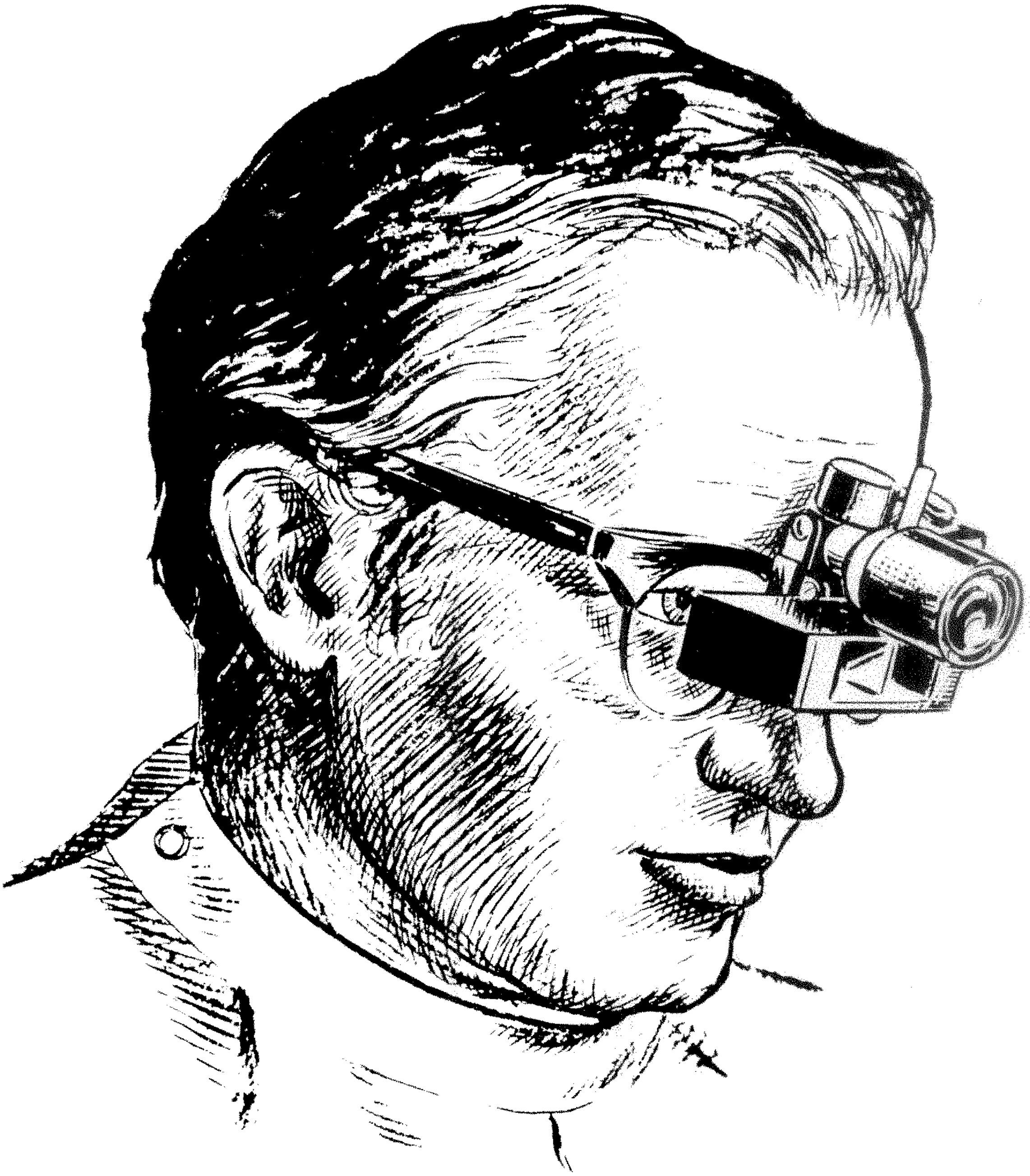

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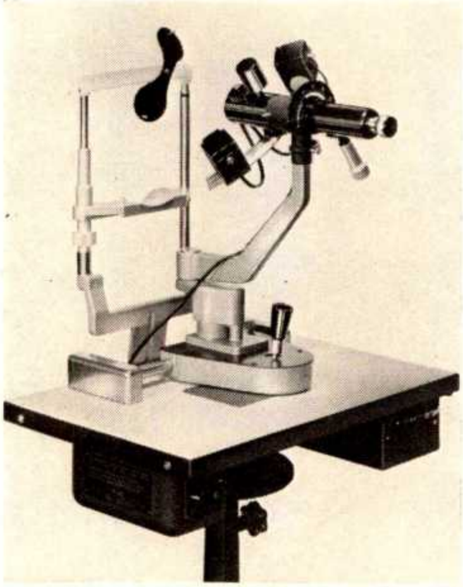

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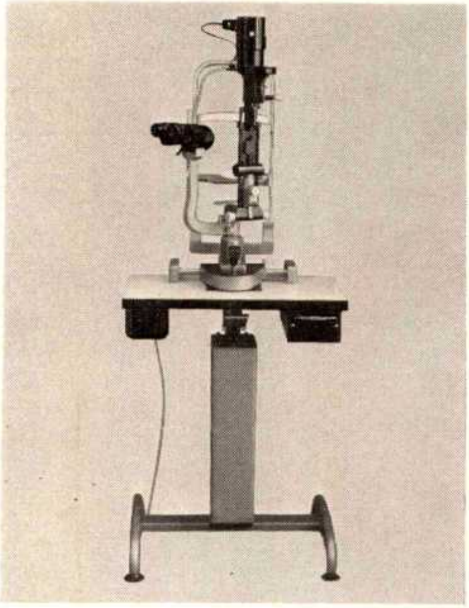

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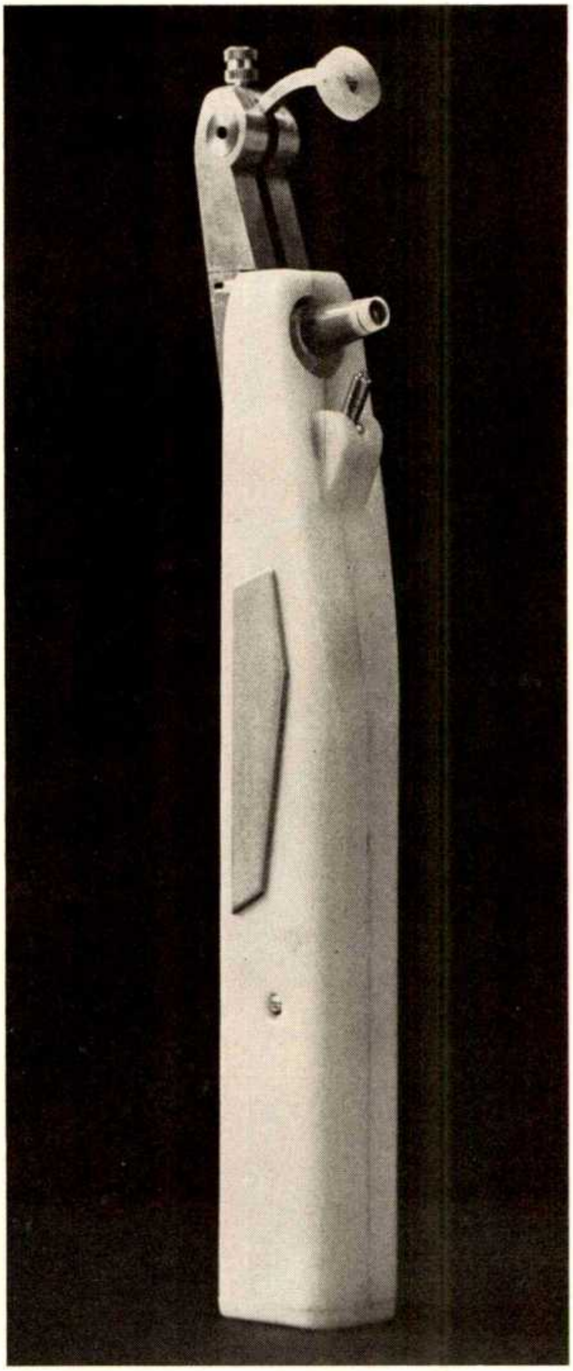

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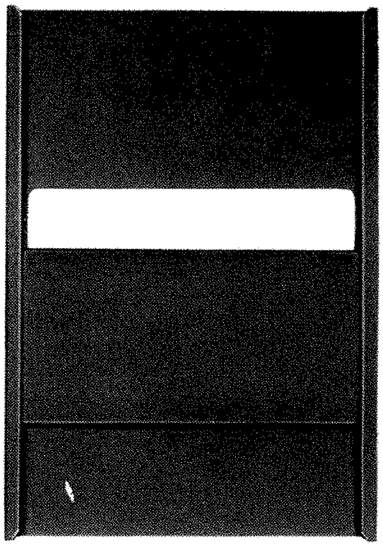

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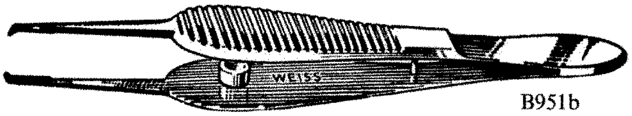

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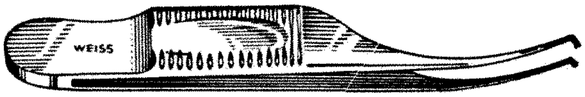

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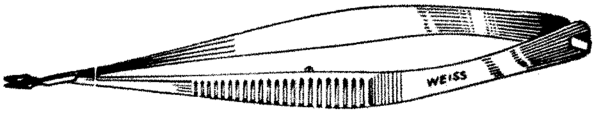

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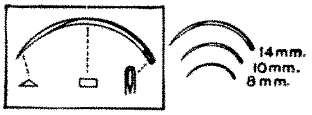
B1053. **Scissors,** miniature, for removal of corneal sutures, etc.



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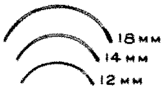

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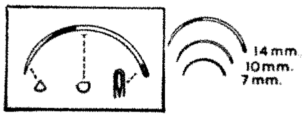

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Brit. J. Ophthal. (1971) **55**, 289

Communications

Electron microscopical study of Coats's disease

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RAMESH TRIPATHI AND NORMAN ASHTON
Department of Pathology, Institute of Ophthalmology, University of London

At the present time there is only one report in the literature on the ultrastructural changes to be found in Coats's disease and this is limited to a description of subretinal and intraretinal "ghost cells" (Manschot and de Bruijn, 1967). We have recently had an opportunity to carry out an electron microscopical examination of an early, typical case and, although our findings add little to existing knowledge of the aetiology of the condition, they are of value in interpreting the morbid histological appearances of conventional microscopy and in understanding its pathogenesis.

Case Report

A female child was referred to hospital with a 6-month history of a white pupil and divergent squint in the right eye. The child was otherwise healthy and there was no relevant family history. Examination under general anaesthesia revealed extensive retinal detachment and a dense white plaque in the macular area. The left eye was normal. Retinoblastoma was diagnosed and the eye enucleated.

Pathology

MATERIAL AND METHODS

The globe was immediately bisected through the ora serrata and both the anterior and posterior segments were placed in 2·5 per cent. buffered glutaraldehyde solution.

Macroscopically, the anterior segment showed no abnormality and there was no evidence of a tumour within the posterior segment, where the white plaques seen clinically could now be identified as intraretinal exudates. There was widespread thickening and opacification of the retina and this was particularly evident at the posterior pole and at the temporal periphery, where dense yellowish-white intraretinal exudates could be seen in intimate relation to dilated, irregular, and aneurysmal vessels. The latter area, together with the underlying choroid and sclera, was selected for both light and electron microscopical examination (Fig. 1). Another section of the retina was removed for trypsin digestion, but this failed owing to the glutaraldehyde fixation.

Electron microscopy

Small blocks of tissue from the retina, choroid, ciliary body, iris, trabecular meshwork, and cornea were dissected and post-fixed in one per cent. osmium tetroxide solution for electron microscopy. After dehydrating in ascending grades of ethanol and clearing in epoxy-propane, the tissue blocks were embedded in Araldite and sections were cut on a Huxley ultramicrotome. Thick sections (1–2 microns) for light microscopy were stained with toluidine blue. Thin sections (500–800 Å) for electron microscopy were stained with uranyl acetate and lead citrate. Electron micrographs were taken with an AEI EM6 electron microscope.

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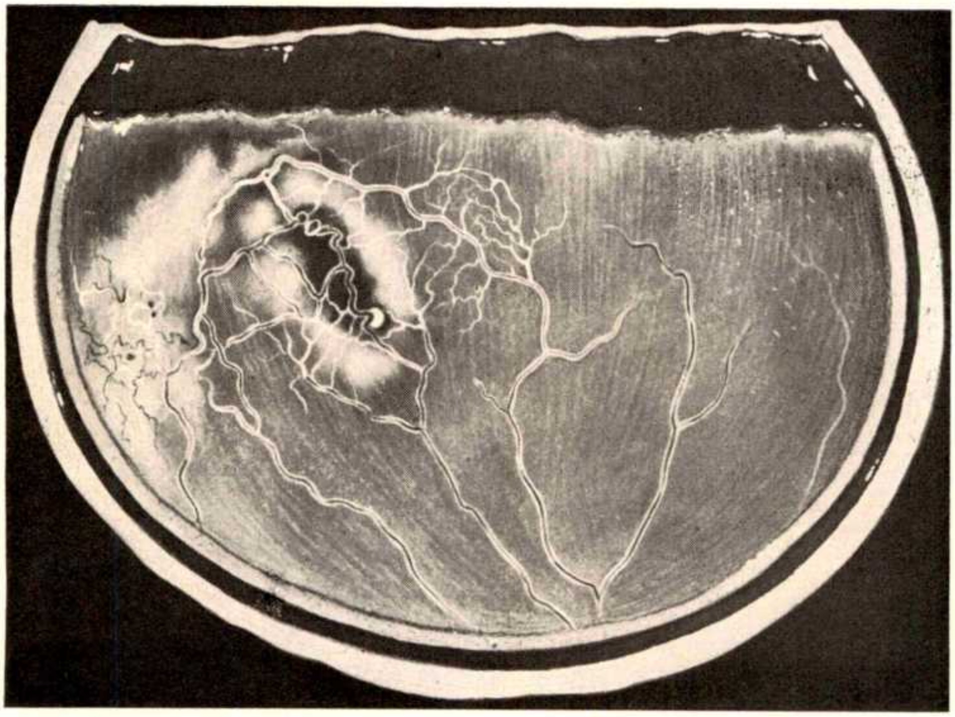

FIG. 1 *Painting of segment of open eye, showing exudates at the temporal periphery intimately related to dilated, irregular, and aneurysmal vessels. This area was selected for light and electron microscopical examination*

FINDINGS

Histological

Sections showed a pronounced and irregular thickening of the retina, which, in the areas examined by light microscopy, showed no evidence of detachment. The thickening was attributable (*a*) to massive exudation with the formation of cystic cavities containing eosinophilic fluid in the inner retina; (*b*) to a heavy infiltration of the retina with foam cells and "ghost cells" particularly in the inner layers; (*c*) to a diffuse glial proliferation (Fig. 2). Intensely eosinophilic exudates were seen in some parts of the outer retina. These pathological changes had completely disrupted the retina so that its normal architecture was lost (except in some areas where the outer retina was well preserved), the visual cells appearing relatively normal with their outer segments lying directly upon a pigment epithelium showing no abnormality apart from occasional proliferative foci.

All sections showed gross pathological changes in the retinal vessels, many of which were dilated, thick-walled, and surrounded by proliferating glial cells, among which numerous pigment-bearing cells could be seen. Perls's stain for iron pigment gave negative results. Some of the larger vessels showed greatly thickened hyaline walls containing PAS-positive material, small aggregations of red cells, and pigment. Mononuclear and polymorphonuclear cells were present within the lumina of some vessels and were also seen perivascularly together with spindle cells and numerous eosinophils (Figs 2, 3, and 4). Mallory's phosphotungstic acid haematoxylin stain (PTAH) showed fibrin within the deep exudates

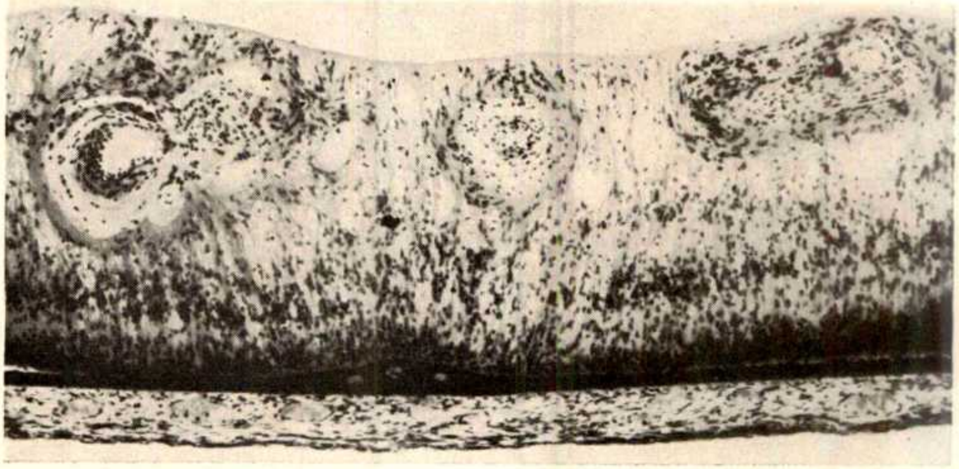

FIG. 2 *Retina greatly swollen by exudate, foam cells, and glial proliferation, with disruption of normal structure. The vessels show gross hyaline thickening, narrowing of their lumina, and perivascular infiltration. The pigment epithelium shows mild proliferative changes. Paraffin section. Haematoxylin and eosin.* ×100

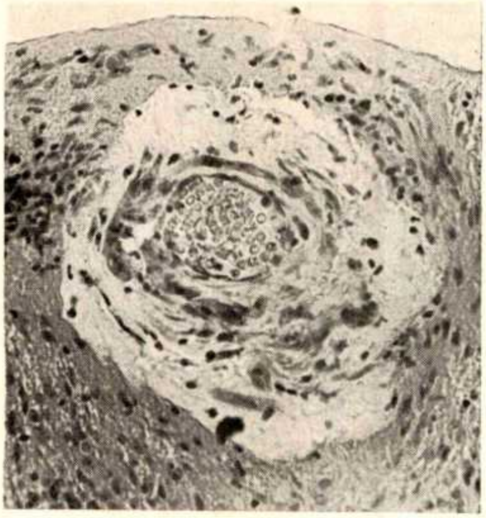

FIG. 3 *Hyalinized vessel, showing a perivascular proliferation of spindle cells and surrounding gliosis. Paraffin section. Haematoxylin and eosin.* ×210

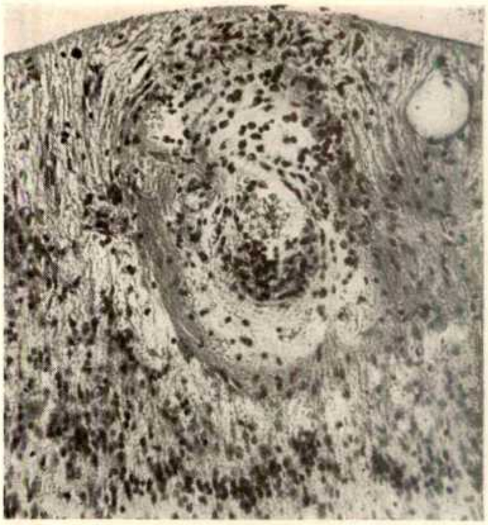

FIG. 4 *Hyalinized vessel, showing inflammatory cells, including eosinophils, within the lumen and perivascularly. Paraffin section. Haematoxylin and eosin.* ×145

and within the cystic cavities. The choroid and sclera were normal. Light microscopy of Araldite sections (Figs 5, 6, 7, and 8, overleaf) confirmed these findings and showed in addition platelet thrombi in some vessels and the presence of large aneurysmal vessels which were devoid of endothelium and lined only with fibrous tissue; they were either empty or contained plasma clot (Figs 7 and 8).

Electron microscopy

Sections of cornea, trabecular meshwork, iris, and ciliary body showed no structural abnormality. Sections of the retina, which included the areas of the lesion, revealed the

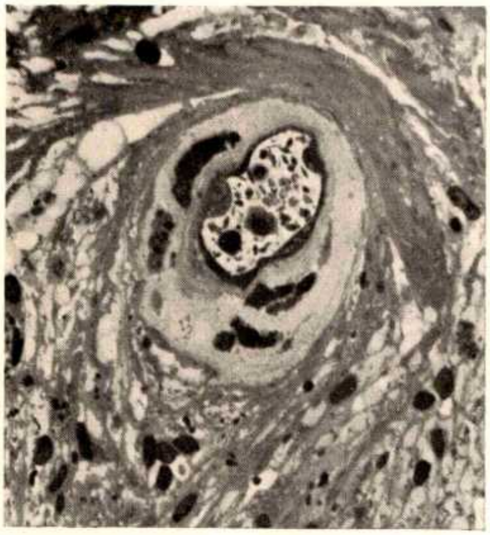

FIG. 5 *Hyalinized vessel, lined with endothelium and containing platelets and red blood cells in the lumen; red cells and pigmented cells are seen in the wall which is surrounded by dense gliosis. Araldite section. Toluidine blue.* ×665

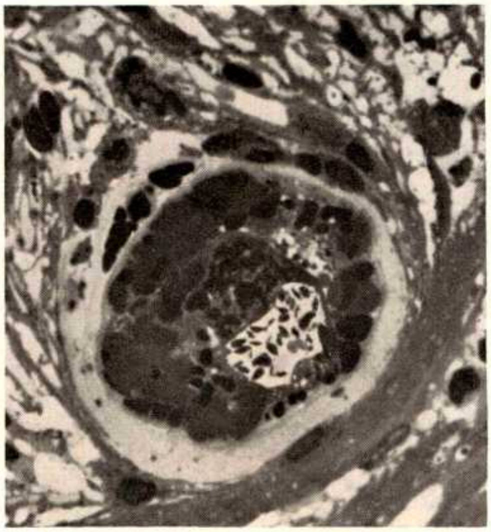

FIG. 6 *Hyalinized vessel similar to that shown in Fig.* 5 *but with extensive haemorrhage in its wall. Araldite section. Toluidine blue.* ×665

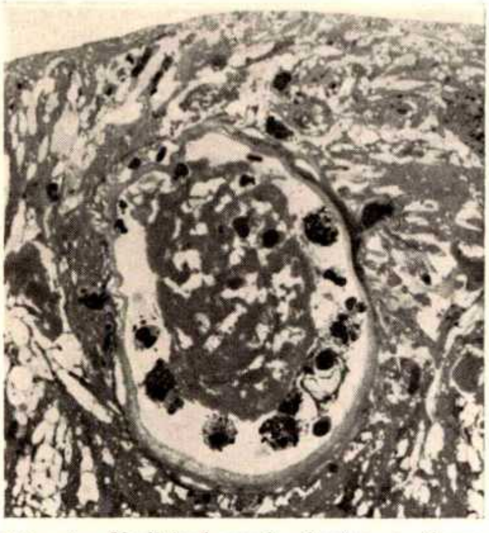

FIG. 7 *Hyalinized vessel, showing a plasma thrombus, loss of endothelium, and pigmented cell infiltration in the wall. Araldite section. Toluidine blue.* ×415

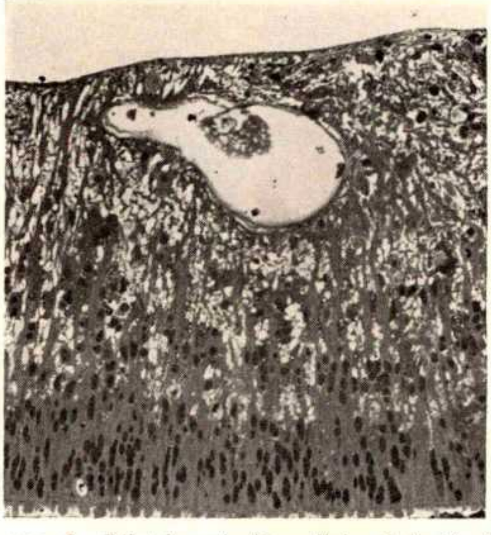

FIG. 8 *Dilated vessel, thin-walled and devoid of endothelium, forming a cyst-like space in the retina, which is densely infiltrated with "ghost cells". Araldite section. Toluidine blue.* ×165

underlying choroid to be essentially normal and Bruch's membrane to be intact. The pathology was confined entirely to the retinal components. The most conspicuous structural alterations were observed in the blood vessels located in the area of retinal thickening, where their walls were mostly greatly thickened and replaced by a laminated fibrous coating consisting mainly of basement membrane-like material infiltrated with

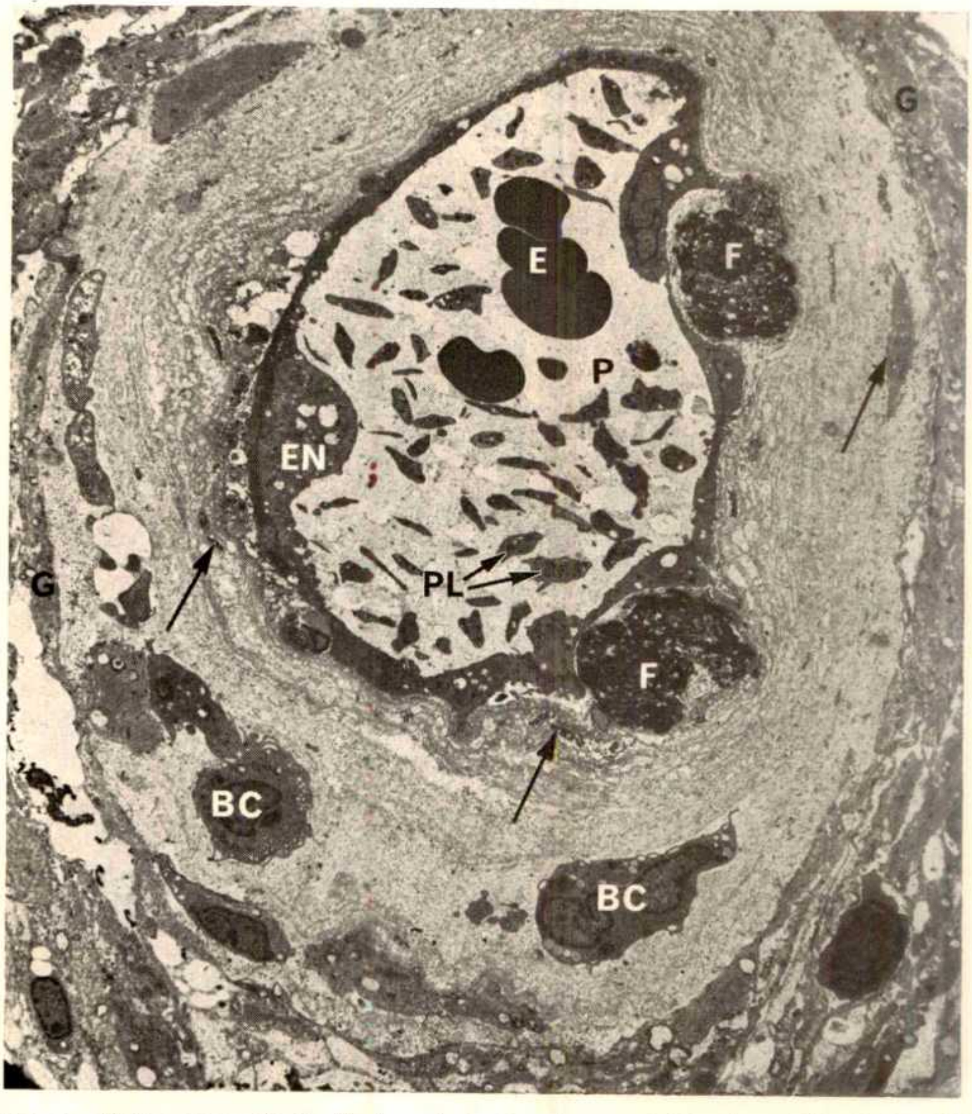

FIG. 9 *Electron micrograph of a blood vessel, showing a lumen containing plasma (P), platelets (PL), and erythrocytes (E). The vessel wall is here represented by a laminated fibrous coat infiltrated with plasma, blood corpuscles (BC), and some cellular debris (arrowed). Note that the endothelium (EN) is still continuous, although collections of fibrin (F) in the subendothelial space are apparent. G = Perivascular glia. Approx.* ×3,650

serofibrinous exudates, blood corpuscles, and some cellular remains (Figs 9, 10, and 11). An intact endothelial lining was observed in some vessels (Figs 9 and 10), but the majority were completely devoid of endothelium and pericytes; blood corpuscles, plasma, and fibrin filled the lumina of these vessels (Figs 11, 12, and 13). The more dilated or aneurysmal and telangiectatic vessels showed an irregular wall invariably infiltrated with plasmoid and fibrinous material (Figs 12 and 13). In places this fibrous wall was extremely thin or even absent and the lumen extended up to the basement membrane of the surrounding glial cells (Fig. 12). The external limit of the vessel wall in most cases was demarcated from the surrounding retina solely by a thin basement membrane anchored to the sur-

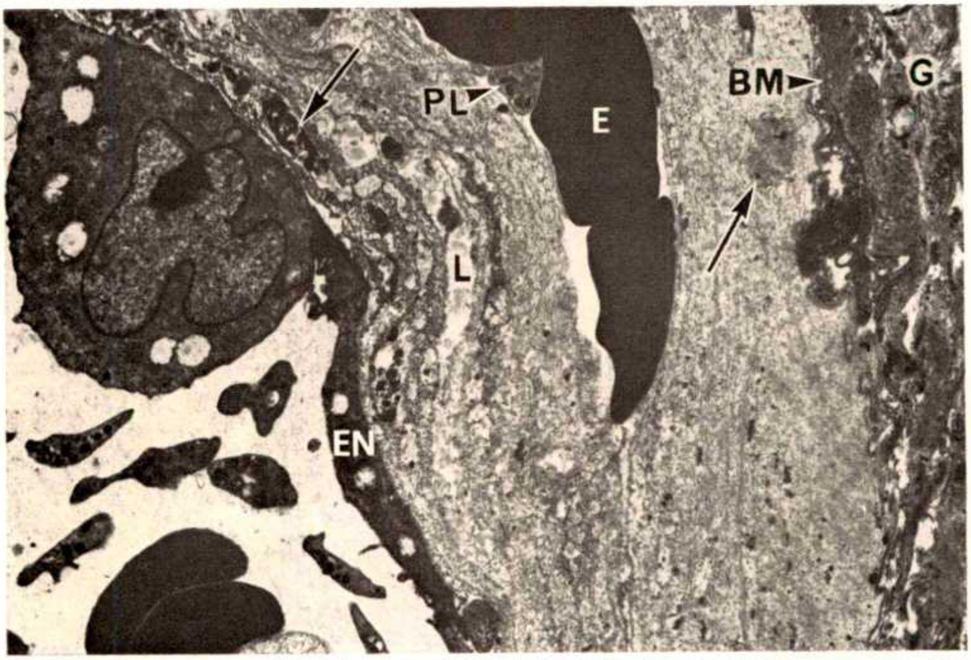

FIG. 10 *Electron micrograph of the wall of a blood vessel, showing a laminated arrangement of basement membrane-like material infiltrated with erythrocytes (E), platelets (PL), lipid droplets (L), and some cellular debris (arrowed). The endothelium (EN) is showing cystic changes in the mitochondria. The external limit of the vessel wall is demarcated by the basement membrane (BM) of the surrounding glia (G). Approx.* ×6,650

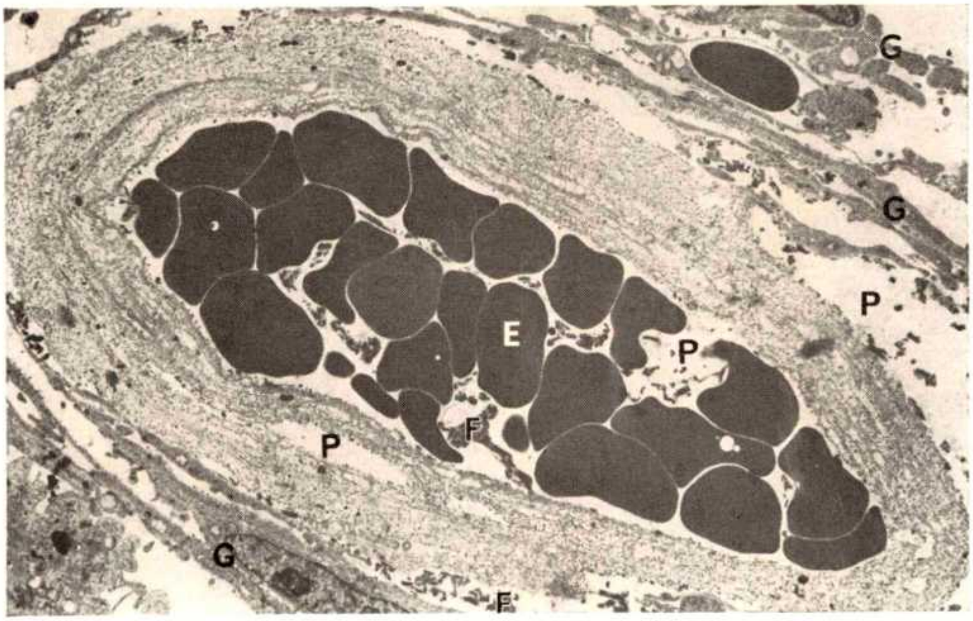

FIG. 11 *Electron micrograph of a blood vessel in the retina containing erythrocytes (E), plasma (P), and fibrin (F), and showing a total absence of the vascular endothelium; the vessel wall is represented by a laminated fibrous coat only. Note the plasmoid (P) and fibrinous (F) transudates both within and outside the vessel coat and the perivascular mantle of glial cells (G). Approx.* ×2,400

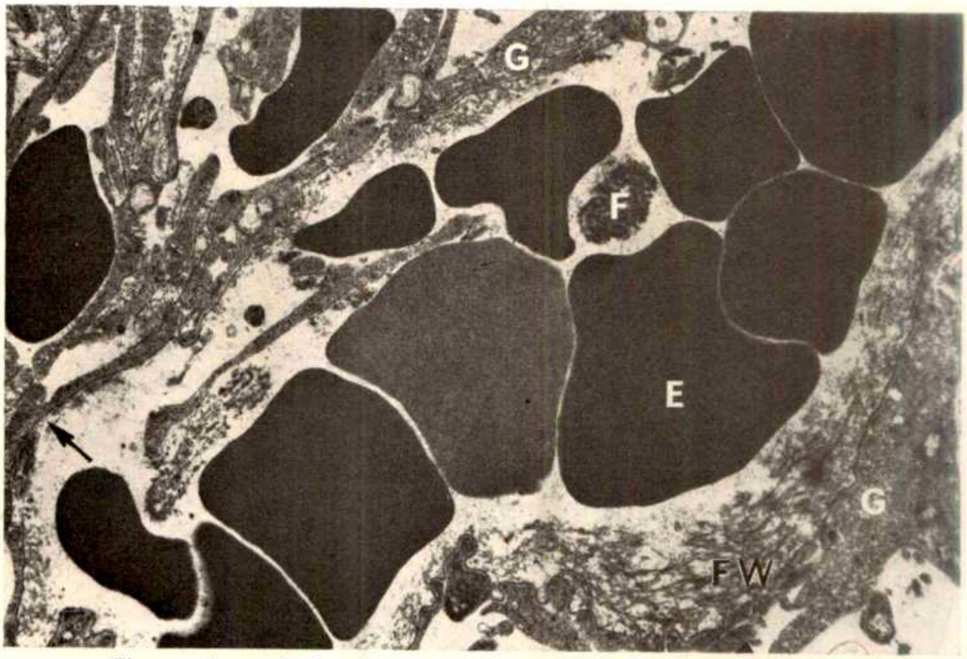

FIG. 12 *Electron micrograph of a telangiectatic blood vessel, showing erythrocytes (E) and fibrin (F) in the lumen. Note the extension of the lumen in some places (arrow) up to the basement membrane of the surrounding glial mantle (G), while in other places fibrous remnants of the wall (FW) intervene between the two. Approx.* ×6,650

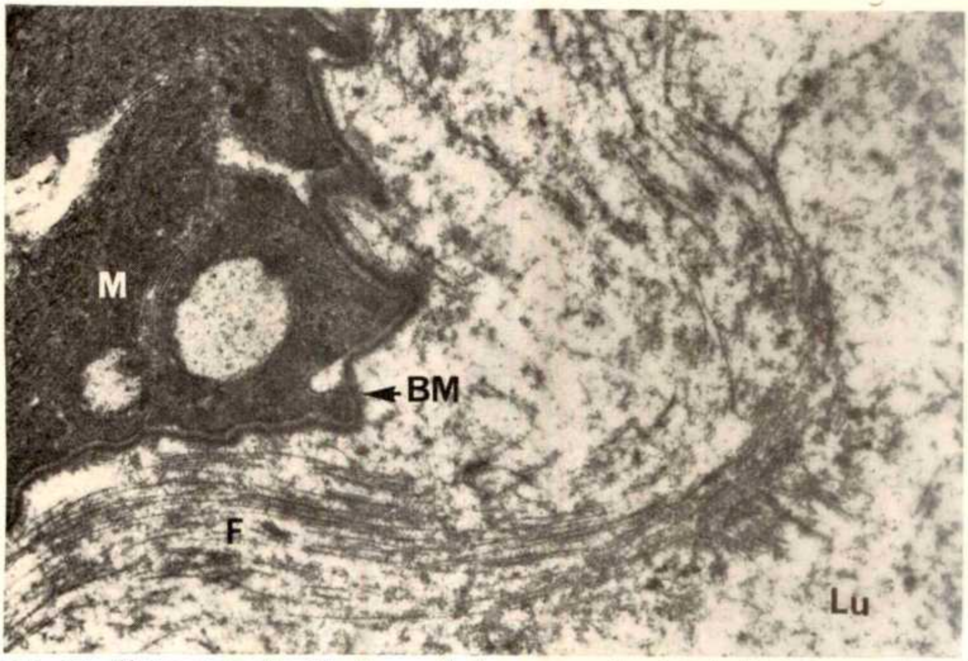

FIG. 13 *Electron micrograph of the fibrous wall of an aneurysm, the extent of which is demarcated by an electron dense basement membrane (BM), presumably formed by the surrounding Müller cells (M). Note the presence of plasmoid material within the lumen (Lu) and also in the fibrinous wall (F), the latter consisting of basement membrane material and fine fibrils (approximately* 100 Å *in diameter and having a beaded pattern along the long axis).* ×16,650

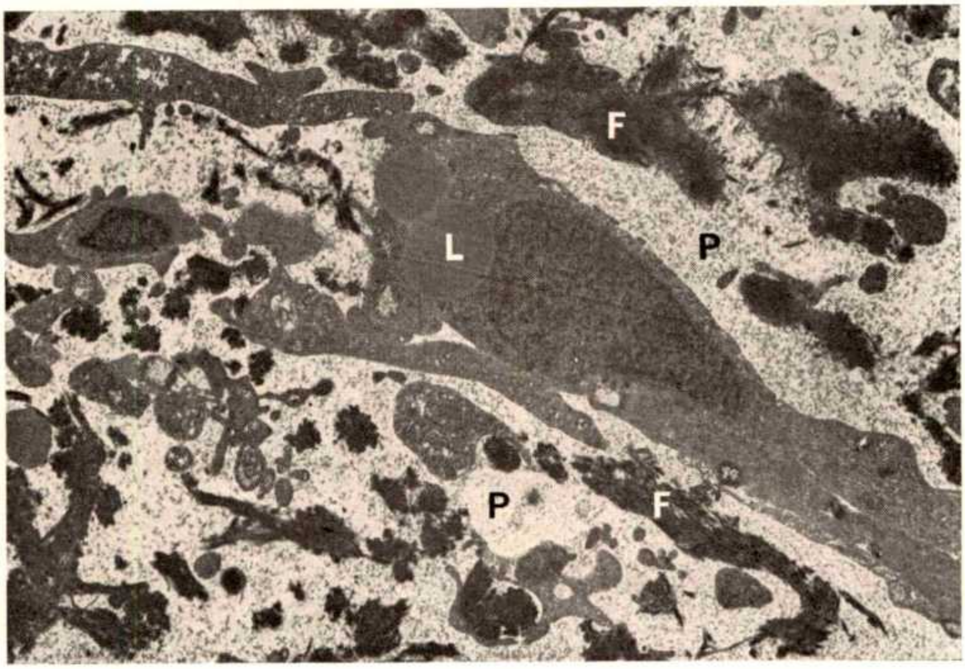

FIG. 14 *Survey electron micrograph of the intraretinal exudates, showing plasmoid* (*P*) *and fibrinous* (*F*) *materials. Note also the lipoidal inclusions* (*L*) *in a Müller cell.* ×4,000

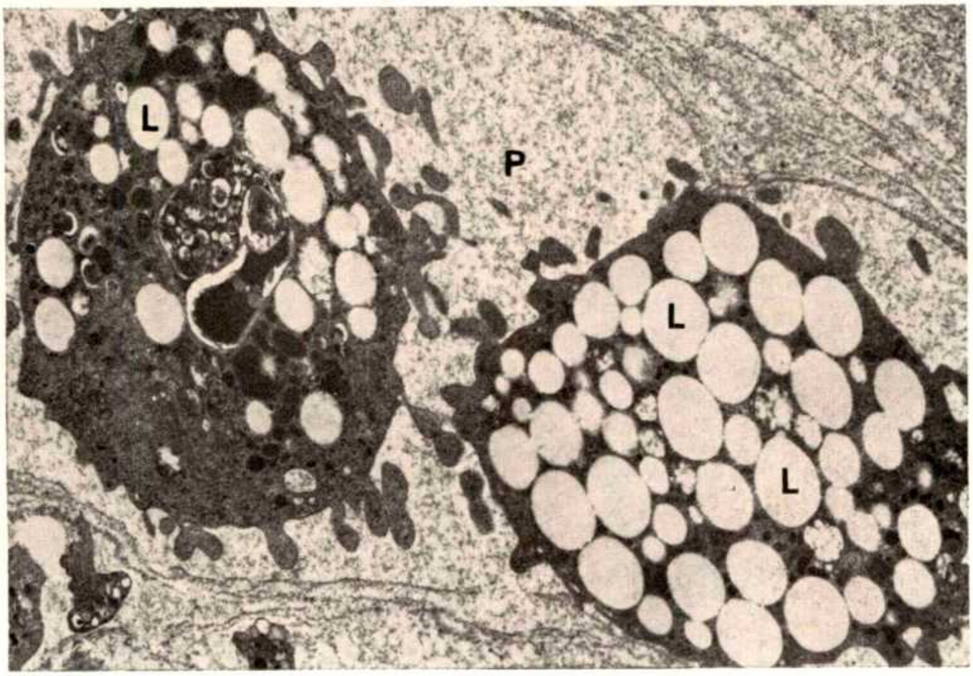

FIG. 15 *Electron micrograph of intraretinal macrophages ("foam cells"), showing oval or circular electron optically empty spaces* (*L*) *which were originally occupied by lipid droplets.* *P* = *Plasmoid exudate.* ×8,000

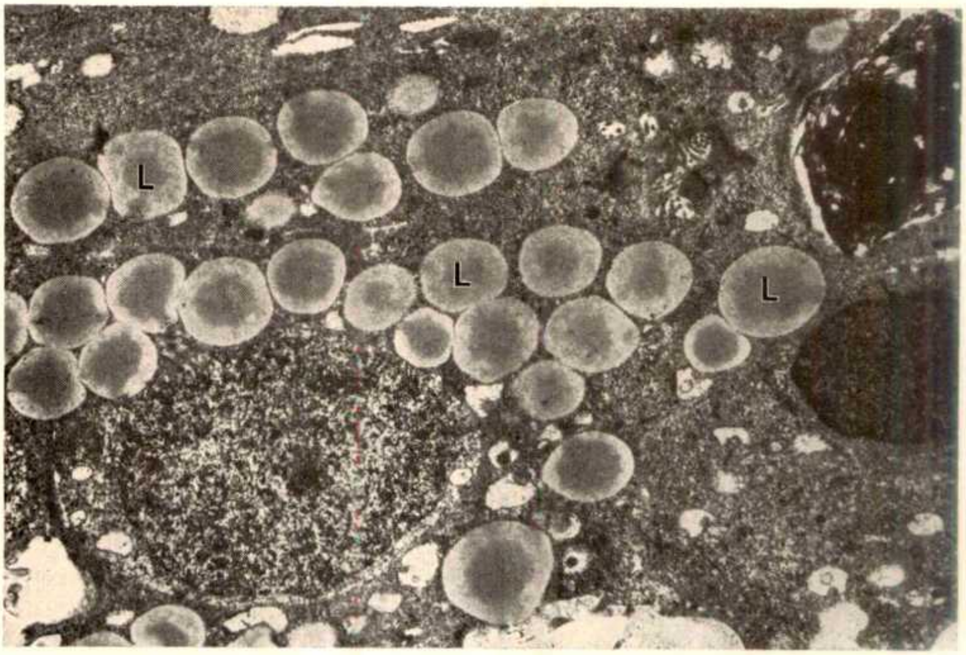

FIG. 16 *Electron micrograph of a macrophage ("foam cell"), showing intracellular lipoidal inclusions (L).* ×6,600

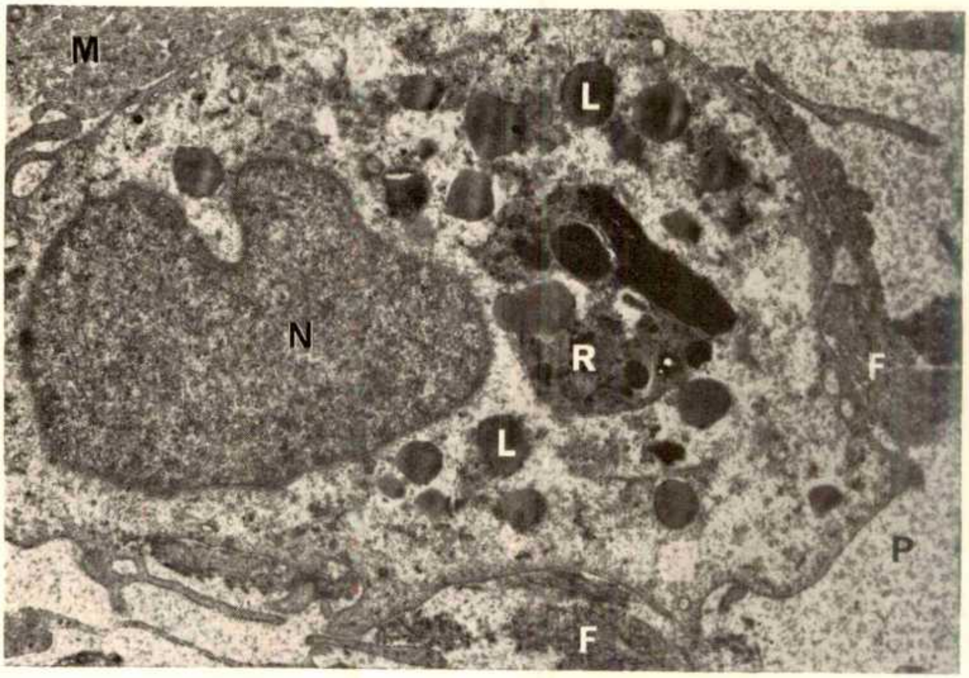

FIG. 17 *Electron micrograph of an intraretinal macrophage, showing intracellular lipoidal inclusions (L), residual bodies (R), and nucleus (N). Note also the surrounding plasmoid (P) and fibrinous (F) exudates and Müller cell (M).* ×10,000

rounding glial cells (Fig. 13). In some instances, however, the existence of a blood vessel or aneurysm was recognized only by the presence of a space filled with plasma, fibrin, blood corpuscles, and macrophages, and incompletely surrounded by a basement membrane of the adjacent glial cells. No new vessels were found as described by Wise (1961).

Although the structural disorganization involved the entire area of the retinal lesions studied electron microscopically, it was most marked in the anterior layers (*i.e.* nerve fibre, ganglion cell, and inner nuclear layers), the elements of which were much reduced in number. In other areas the retina was greatly thickened because of the massive accumulation of plasmoid and fibrinous exudates (Fig. 14) and occasional blood corpuscles. The visual elements showed patchy degenerative and atrophic changes, which extended into the outer nuclear layer to a minor degree. The external limiting membrane appeared generally intact. The pigment epithelium showed occasional focal proliferative changes and in places was separated from the nervous components of the retina. The subretinal space appeared electron-optically empty, except for occasional cellular fragments of visual elements, pigment epithelium, a thinly distributed plasmoid material, and a few foreign cells.

The nervous layers of the retina were infiltrated by foam and "ghost" cells and macrophages (Figs 15, 16, and 17), although the maximum infiltration was seen in the middle and anterior layers. The majority of the macrophages contained lipoidal globules and a few also contained clumps of pigment granules, which in some sections appeared indistinctly membrane-bound and were probably secondary lysosomes (Fig. 17). The Müller cells in some areas appeared hypertrophic and generally showed an increase in intracellular fibrils and rough surface endoplasmic reticulum; in many places, however, the cellular architecture was destroyed. There was a striking perivascular proliferation of glial cells.

Discussion

The passage of large colloidal particles into the delicate tissues of the central nervous system, as occurs in plasmatic exudation, disrupts the organization of the nervous elements and severely impairs their function. It is, therefore, clearly essential that these tissues should be protected from their entry, and in the case of the retina this is normally achieved by two barrier systems, one located in the inner retina, apparently at the level of the vascular endothelium (Ashton, 1965; Cunha-Vaz, Shakib, and Ashton, 1966) and the other in the outer retina at the level of the pigment epithelium. Breeching of either of these two barriers results in subretinal and/or retinal exudation and, although the resulting clinical and pathological pictures vary according to the location, extent, severity, and chronicity of the exudative process, they are distinct pathogenetically only as regards the cause of the initial leakage. There is no doubt that Coats's disease is an example of such a barrier break-down, and, since the classical paper by Reese (1956), it has been generally accepted that this is due to retinal telangiectasis, but the exact cause of this anomaly is still obscure (Manschot and de Bruijn, 1967); a genetic basis has been suggested (Small, 1968). Although in the past there has been considerable controversy, admirably summarized by Woods and Duke (1963), few would disagree today that all the pathological changes – intraretinal and subretinal exudation, haemorrhages, lipid and fibrin deposition, phagocytic proliferation ("ghost cells"), and ultimate glial and fibrous tissue organization – most probably stem, directly or indirectly, from the abnormal vascular permeability. Since the exudates arise in the inner retina from a non-inflammatory vascular disease, as in hypertensive and diabetic retinopathy, it is now apparent that as regards pathogenesis Coats's disease was inappropriately termed "external exudative retinitis."

This present examination of the ultrastructure of a single and very early case of Coats's disease (no subretinal organization or cholesterol depositions being present), while not revealing the cause of the condition, permits comment on a number of its important aspects and suggests a sequence of the pathological changes.

The prominent vascular abnormalities varied from a gross thickening of the walls of the smaller vessels with relatively normal or slightly dilated lumina and continuous endothelium, to a gross thinning of these walls with irregular and dilated lumina and a total absence of the endothelial lining. The lumina in both instances contained impacted red cells, plasma, thrombi, or platelet aggregations. By electron microscopy the mural thickening was found to be due to insudated lipid, plasma, and fibrin, together with abundant basement membrane-like material, cellular debris, and leucocyte and macrophage infiltration. Initially, the leakage of plasma into the vessel wall must occur through the endothelium but this, although showing degenerative changes as evidenced by cytoplasmic vacuolation, was frequently seen to be continuous with its junctions intact. At a later stage the endothelium was entirely absent and the vessel wall came to consist solely of a thick laminated coat of plasmoid and fibrillar elements, immediately surrounded by glial cells. It is not surprising that a vessel walled by such an acellular porous membrane should become aneurysmal or telangiectatic and permit a continual outpouring of its contents, including the occasional haemorrhage, into the adjacent tissues. Finally, the walls of these telangiectatic vessels may absorb leaving the basement membrane of the surrounding glial cells to form a channel for the blood; at this stage extensive haemorrhage may occur and organization follow. These pathological changes, therefore, suggest that an early event in Coats's disease is abnormal endothelial permeability; whether this is primarily due to a deficiency in structure or function, that is a failure to provide the normal blood-retinal barrier, is not at present clear, but it would seem that both the telangiectasis and leakage may be secondary to it. On such a basis there would be no difficulty in accepting Coats's Groups I and II, that is cases of exudative retinopathy with and without obvious vascular changes, as stages of the same condition.

The presence of basement membrane-like material and blood components in the thickened vascular walls explains the brilliant PAS-positive staining seen by light microscopy, which was originally noted by Reese (1956) and confirmed by Duke and Woods (1963), Manschot and de Bruijn (1967), and many others. The exudates in the retina also stain positively with PAS but less intensely.

Very similar – and sometimes identical – ultrastructural appearances of stratified or laminated mural thickening with fibrillar material, have been described in a number of other conditions in which increased vascular permeability is known to occur or might be supposed to be a factor. Examples are to be found in diabetic retinal microaneurysms (Toussaint and Dustin, 1963; Bloodworth, 1964), in diabetic vessels in the kidney (Bergstrand and Bucht, 1959) and toe (Banson and Lacy, 1964), and in the retinal vessels of diabetic dogs (Bloodworth and Molitor, 1965), in small vessels from a healed cornea (Szalay and Pappas, 1970), and in renal (McGee and Ashworth, 1963) and experimental hypertension (Ashworth and Grollman, 1959). These appearances have ususally been described simply as "basement membrane thickening", but one wonders to what extent the mural thickening may be attributable, as in Coats's disease, to an abnormal endothelial permeability to protein.

The extension of exudate into the retina itself, causing disruption of its structure and wide separation of the cellular membranes to form large extracellular spaces containing plasma, fibrin, erthrocytes, leucocytes, and macrophages, is completely non-specific in character. Such ultrastructural appearances have already been described in the brain (Lampert and Carpenter, 1965; Bubis and Luse, 1964) and in the retina in experimental ischaemia (Ashton, 1965; Shakib and Cunha-Vaz, 1966) and experimental hypertensive retinopathy (Ashton, Peltier, and Garner, 1968). The presence of leucocytes around the abnormal vessels and within their walls has also been noted previously, and the first case of Manschot and de Bruijn (1967) also showed eosinophils as in our case; this is probably no more than a mild low-grade inflammatory reaction to the exudation.

We agree with Manschot and de Bruijn (1967) that haemorrhages are not an essential feature as originally thought by Coats (1908) and subsequently doubted by Leber (1916), and would add that the deposition of cholesterol crystals, although highly characteristic, may also be absent, being rather a measure of the severity or chronicity of the exudative process than a specific feature.

As regards the "ghost cells" seen so typically in Coats's disease, there is controversy about their origin, there being two main schools of thought: (*i*) that they originate from retinal histiocytes (macrophages) and (*ii*) that they derive from pigment epithelium. Manschot and de Bruijn (1967) favour the latter origin and, although allowing that some subretinal macrophages may have migrated from the retina, do not refer to them as "ghost cells". These authors differentiate on an ultrastructural basis macrophages containing ingested pigment from pigment epithelial cells which have become phagocytic, *i.e.* ingested pigment is contained in a vacuole whereas native pigment lies free in the cytoplasm. Unfortunately, in pathological material, we have not found this a valid distinction, for on the one hand vacuolar membranes around ingested pigment may be lost in the degenerating macrophage, and on the other hand native pigment may come to lie in pathological vacuoles in the proliferating pigment cell.

Another difficulty is that proliferating pigment epithelial cells may fail to form new pigment (Gloor, 1969) and, to add to the confusion, glial cells have some role in phagocytic activity and may also become laden with lipid, as already observed by Shakib and Ashton (1966) and further confirmed by this present study. In a previous communication from this department, we discussed the origin of retinal macrophages at some length and gave reasons for supposing that they originate both from the local proliferation of resting macrophages in the retina itself (cells which gained access to the retina at the time of vascularization), and from a contribution of similar cells from the blood stream, when the blood-retinal barrier is deficient (Shakib and Ashton, 1966), as in Coats's disease. We believe, in common with Marshall and Michaelson (1933), that the majority of "ghost cells" are lipid-laden macrophages, which have arisen in the above two ways, especially as in our present case proliferation of the pigment epithelium was minimal and in some areas, where "ghost cells" were prolific, this layer even appeared quite normal. There is no doubt, however, that pigment cells have phagocytic properties, as demonstrated by Young and Bok (1969) in the case of rod outer segments, and it is well known that they can proliferate and invade the retina to assume the appearance of macrophages, as recently shown in photocoagulation experiment on rabbits (Gloor, 1969). It may be concluded, therefore, that in cases where the pigment epithelium becomes involved in the exudative injury its cells may contribute to the macrophage reaction of the retina ("pigment epithelial macrophage" of Gloor, 1969), and so to the "ghost cell" population, but when this stage is reached they cannot be separately identified. It would also be generally agreed that pigment epithelial cells, together with fibroblasts from the retina, form the subretinal fibrous tissue, but since this was absent in our present case it provides no further evidence in this direction.

Summary

An ultrastructural study of an early case of Coats's disease confirms the widely-held view that an abnormal permeability of the retinal vessels is fundamental in its pathogenesis. It is suggested that the pathological changes may initially derive not from telangiectasis, but from a functional or structural breakdown of the blood-retinal barrier (vascular endothelium), giving rise to plasmatic vasculosis and mural disorganization, and that these result in aneurysmal dilations and telangiectasis. Leakage of blood components then increases to form intraretinal and subretinal exudates, haemorrhages, lipid and fibrin deposits, with phagocytic proliferation, disorganization and destruction of the retinal elements, and eventually glial and fibrous tissue organization.

The characteristic profusion of macrophages and "ghost cells" within the affected areas is most likely due to the local proliferation of resting histiocytes in the retina itself, augmented by blood-borne macrophages and migrating pigment epithelial cells.

It is a pleasure to acknowledge the technical assistance of Mr. G. E. Knight and Mr. V. Elwood and the secretarial help of Miss. K. O'Malley.

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Chronic progressive external ophthalmoplegia and pigmentary degeneration of the retina

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The rare association of external ophthalmoplegia and ptosis with pigmentary degeneration of the retina was first described by Barnard and Scholz (1954) in a report of four cases. The subsequent literature was reviewed by Davidson (1960), who found that only eighteen cases had been described, and added one further case. Within this series he was able to define a relatively homogenous group of twelve cases. They manifested a syndrome characteristically occurring in females with the onset of ptosis in childhood and of external ophthalmoplegia in adolescence or early adult life. The pupils were normal and an atypical retinitis pigmentosa was present with normal retinal vessels and optic discs. The visual fields were variable showing either no defect, peripheral contraction, or the characteristic annular scotoma of retinitis pigmentosa.

The present communication reports two further cases of this rare syndrome and reviews the relevant literature subsequent to 1960. Serum enzyme studies in eleven other patients with progressive external ophthalmoplegia unassociated with pigmentary degeneration of the retina are also reported and the findings discussed.

Case reports

Case 1, a girl now aged 14 years, was first seen by one of us (D.S.T.) when aged 6 years. She was initially referred for an eye examination because she was observed to hold books close to her eyes. The uncorrected visual acuity was 6/9 in each eye and widespread pigmentary changes were noted in both fundi. The child was underweight and enuritic. The Wassermann reaction was negative. When aged 10 she was noted to have a mild bilateral ptosis which was not improved by an injection of Tensilon, and a year later, because of her poor physical development, she was investigated as a possible case of Turner's syndrome, but chromosome studies ruled this out. By age 13 the ptosis had increased markedly and bilateral symmetrical limitation of ocular movements, especially elevation, was observed, but no diplopia was elicited. At this stage she was also noted to be incoordinated and ataxic, falling frequently when tired.

She has one normal brother aged 9 years and the mother's fundi are normal. There is no known history of ptosis in the family.

EXAMINATION

She was co-operative and of fair intelligence but markedly undeveloped for her age in height, weight, and secondary sex characteristics (Fig. 1). There was marked symmetrical bilateral ptosis with characteristic frontalis overaction (Fig. 2). The external ocular movements of both eyes were symmetrically limited and elevation was absent. The pupils were normal. The visual acuity of

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the right eye was 6/9 with +1 D cyl., axis 168°, and of the left eye 6/12 with +0·5 D cyl., axis 20°. Fundus examination showed clumping of the retinal pigment, which was coarse at the periphery but finer posteriorly, producing a dust-like appearance. The choroidal vascular pattern was visible (Fig. 3). The discs were normal and the retinal arterioles of normal calibre. The visual fields were full (2 mm. white target at 1/3 metre).

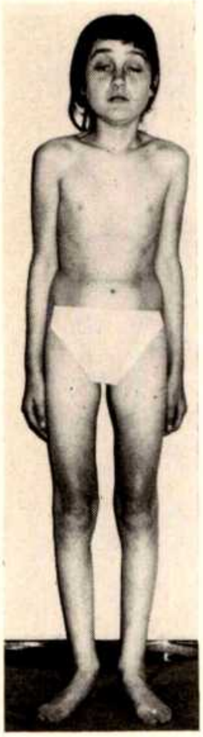

FIG. 1 *Case* 1. *Full frontal view to show retarded development*

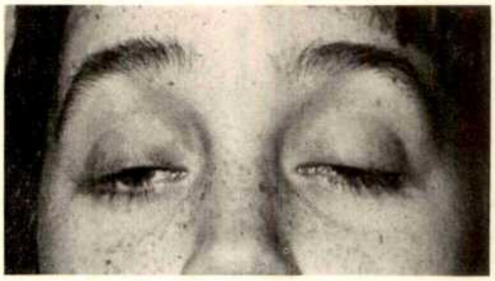

FIG. 2 *Case* 1. *Facial view to show ptosis*

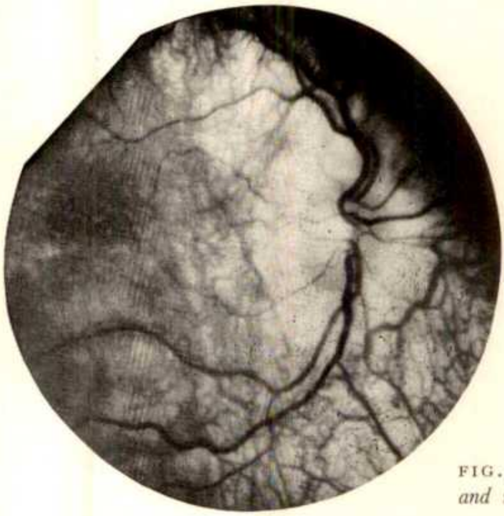

FIG. 3 *Case* 1. *Right disc and macula*

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Speech and hearing were normal and examination of the cranial nerves revealed no abnormality. The general skeletal musculature was poorly developed and the muscle tone flaccid. In the upper limbs there was symmetrical muscle weakness, ataxia, dysdiadochokinesis, and a gross intention tremor. The lower limbs also showed poor muscle power and marked ataxia. She was unable to walk along a straight line and could not stand with feet together and eyes closed. The deep tendon reflexes were all present but diminished and the plantar responses were weak flexor. No sensory disturbance was detected.

INVESTIGATIONS

Blood: Hb and white blood cells normal; the blood film showed no acanthocytosis or other abnormality; serum aldolase 7S-L units/ml. (normal range 3–8); serum creatine phosphokinase 6·0 Sigma units (normal range 0–12); electrophoresis showed no betalipoproteinaemia or other abnormality; Wassermann reaction negative; serum cholesterol 195 mg. per cent.; protein bound iodine 4·9 μg. per cent.

Urine: No albumin or sugar present.

Radiology: Skull *x* ray normal; skeletal maturation consistent with chronological age.

Buccal smear: 33 per cent. Barr bodies.

Cerebrospinal fluid: Clear and colourless, pressure normal; protein 130 mg./100 ml.; glucose 121 mg./100 ml.; chloride 40 mEq/l; cells 10 red blood cells/c.mm.

Tensilon and prostigmine: Tests negative.

Electroencephalogram: Partial right bundle branch block and a frontal plane QRS axis of minus 90°. Occasional extrasystoles (Dr. James Wilkinson).

PROGRESS

During the past 12 months the ataxia has increased and she now has difficulty in walking across a room. She spends most of her day in a wheelchair.

Ptosis crutch glasses have been tried but she has found them too painful to wear regularly.

Case 2, a girl aged 14 years, was first seen by one of us (P.V.M.) when she complained of difficulty in reading small writing, though the most obvious abnormality was gross drooping of both upper eyelids. This abnormal appearance had developed during the preceding 3 years. She had had several episodes of red eye in the same period treated with ointment by her doctor. No double vision had occurred.

The patient has one normal brother aged 7 and both parents' fundi are normal. There is no family history of eye disease.

EXAMINATION

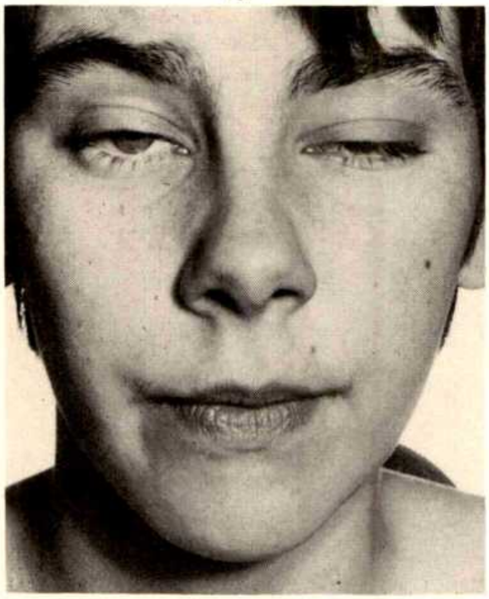
She was co-operative and of normal intelligence. Marked bilateral ptosis was present with poor action of the levators and overaction of the frontalis muscles (Fig. 4). The external ocular movements of both eyes were limited in all directions and elevation was absent. No weakness of the orbicularis oculi was evident. The pupils were normal. The right eye was emmetropic and had a visual acuity of 6/9. The visual acuity of the left eye without correction was 6/9 and refraction showed + 1·25 D sph. Marked clumping of the retinal pigment was present over the whole of both fundi, the clumping being more coarse at the posterior poles and in the periphery than in the equatorial region (Fig. 5). The optic discs and retinal vessels were normal. The visual fields were full (1 mm. white target at 1/3 metre).

A mild myopathic weakness was present with definite weakness of the flexors of the neck and her general skeletal musculature was thin. In the upper limbs there was ataxia, dysdiadochokinesis, and an intention tremor. The lower limbs were also ataxic and her gait was unsteady. Deep tendon reflexes were absent in the upper limbs while in the lower limbs they were brisk. The plantar responses were flexor. No sensory disturbance was detected.

INVESTIGATIONS

Blood: Hb, white blood cells, blood film, erythrocyte sedimentation rate, serum sodium, potassium, urea, acid and alkaline phosphatase all normal; no serum phytanic acid detected; Wassermann reaction, Reiter protein complement-fixation test, and Kahn test negative; total serum protein 7·1 g./100 ml.; serum albumin 4·8 g./100 ml.; electrophoresis: slightly raised gamma globulin; serum creatine phosphokinase 114 mU./ml. (normal 5–30); serum glutamic-oxaloacetic transaminase 26 units/ml. (normal 5–35); serum aldolase 2·2 mU./ml. (normal 0·9–2·5).

(4)



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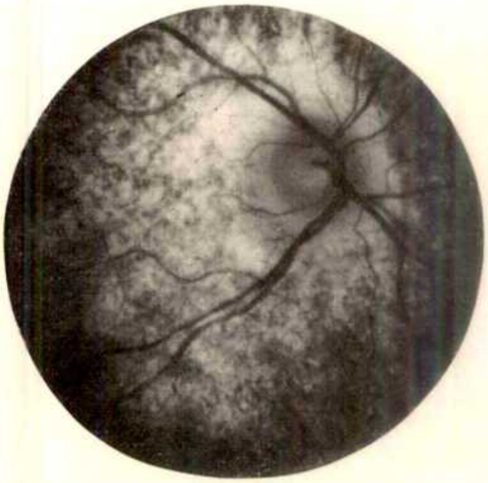

FIG. 4 *Case 2. Facial view to show ptosis*

FIG. 5 *Case 2. Right disc and macula*

Urine: No albumin or sugar present; amino acid chromatography showed normal pattern.

Radiology: Skull, chest, and hand *x* rays normal.

Cerebrospinal fluid: initially blood-stained, subsequently clear and colourless, pressure normal; protein 216 mg./100 ml.; chloride 122 mEq/l.; cells: white blood cells 20/c.mm., red blood cells 481/c.mm.; Lange curve normal.

Electromyography: No abnormality detected in upper and lower limbs; ocular and facial muscles not examined.

Electroencephalograph: normal.

Tensilon test: negative.

Electrocardiograph: Right bundle branch block (Dr. Picton Thomas).

PROGRESS

The left ptosis was treated surgically by a fascia lata (bovine) frontalis sling procedure under general anaesthesia. In spite of the absence of Bell's phenomenon, the postoperative course was satisfactory with only minimal asymptomatic punctate corneal staining with fluorescein adjacent to the limbus inferiorly. The cosmetic result was initially excellent but the left ptosis appeared to have increased again after 4 months. Her condition remains otherwise unchanged.

Discussion

Since Davidson (1960) reviewed eighteen cases showing the association of external ophthalmoplegia and pigmentary degeneration of the retina, adding one case of his own, 21 further cases have been reported in the literature. These, as well as the two cases described in this paper, are summarized in Table I (overleaf).

Table I *Summary of 23 cases with chronic progressive external ophthalmoplegia and pigmentary re*

				Clinical features					
								Muscle weakness	
Authors	*Date*	*Case No.*	*Sex*	*Age at onset*	*Ptosis*	*Ophthalmoplegia*	*Retinal degeneration*	*Orbicularis*	*Facial*
Jampel and others	1961	1	M	48		+	+		
		2	F			+	+		
		3	F	Teens		+	+		
		4	M	Teens		+	+		
		5	F	Childhood		+	+		
		6	M	Teens		+	+		
		7	F	Childhood		+	+		
Walton	1961		F	Childhood	+	+	+		
Harenko and Lappalainen	1962		F	24	+	+	+		
Stanworth	1963		M		+		+		
Thomas, Cordier, Tridon, and Saudax	1963		M	36	+	+	+		
Guerci and Reny	1964		F	25	+	+	+		
Daroff and others	1966		F	11	+	+	+		
Malbrán	1966	1	M	7	+	+	+		+
		2	F	14	+		+	+	+
Shy, Silberberg, Appel, Mishkin, and Godfrey	1967		F	14	+	+	+		
Drachman	1968	1	F	8	+	+	+		+
		2	M	13	+	+	+	+	+
Rosenberg and others	1968	1	M	12	+	+	+	+	+
		2	M	12	+	+	+		
		3	F	7	+	+	+		+
Present cases	1970	1	F	10	+	+	+		
		2	F	11	+	+	+		+

neration

mb	*Shoulder*	*Dysphagia*	*Reduced visual acuity*	*Reduced field*	*Ataxia*	*Deafness*	*Mental change*	*Heart block*	*Raised cerebro-spinal fluid protein*	*Abnormal electro-encephalogram*
			+	+	+					
			+							
			+	+	+					
			+	+	+					
			+		+		+			+
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It is evident that the signs are not usually confined to the external ocular muscles and the retina. Involvement of the muscles of the face, neck, limbs, pharynx, and larynx, ataxia, deafness, mental changes, heart block, raised protein content of the cerebrospinal fluid, and electroencephalographic abnormalities are some of the changes common to many cases. This broad spectrum of associated signs appears to invalidate the concept of Davidson (1960) of an homogenous group, which can be recognized as a syndrome. Drachman (1968) entitled his paper "Ophthalmoplegia Plus" to emphasize the widespread neurodegenerative changes to be found in his four cases, two of which showed the association of external ophthalmoplegia and pigmentary degeneration of the retina. A comprehensive review of 28 cases of progressive ptosis and ophthalmoplegia by Rosenberg, Schotland, Lovelace, and Rowland (1968) included three with pigmentary degeneration of the retina and again illustrated the variety of other signs which may be found in such patients. The two cases reported in this paper also showed changes other than those involving the extraocular muscles and retina. Both had limb weakness, ataxia, heart block, and a raised cerebrospinal fluid protein content, and Case 2 also showed weakness of the facial and neck muscles. Jampel, Okazaki, and Bernstein (1961) reported a Negro family in which seven members had ataxia and other neurological signs associated with retinal changes and an ophthalmoplegia. They also found eight cases in the literature prior to 1960, in which oculomotor palsies, retinal degeneration, and heredo-degenerative ataxia were combined in what they considered to be a single disease entity. In the family they described there were no cases of ptosis, unlike any of the others in Table I, and possibly these seven cases should not be included in that list. They are recorded, however, because they illustrate, together with the others, the diverse neurological associations which may be found in such patients.

It may become possible to classify these apparently heterogenous conditions into syndromes, if underlying defects, such as inborn errors of metabolism, are found to unify them. Refsum's syndrome (Refsum, 1946), for instance, can manifest both a pigmentary degeneration of the retina and a progressive external ophthalmoplegia (Daroff, 1969) as well as other neurological signs, and it appears to be caused by an abnormality of phytanic acid metabolism. Likewise the Bassen-Kornzweig syndrome (Bassen and Kornzweig, 1950), in which similar neurological signs can appear (Daroff, 1969), may be due to a metabolic anomaly relating to the beta-lipoproteins. However, biochemical and haematological irregularities are not necessarily the direct cause of neurological anomalies. In the Bassen-Kornzweig syndrome, for example, it is possible to speculate that the absence of beta-lipoprotein may affect the lipoid structure of the rods and cones; but it is equally likely that the genetic abnormality determining the absence of beta-lipoprotein in the blood may be responsible also for the pigmentary degeneration of the retina (Wolff, Lloyd, and Tonks, 1964). In Refsum's syndrome, however, it has been shown by Eldjarn, Try, Stokke, Munthe-Kaas, Refsum, Steinberg, Avigan, and Mize (1966) that treatment with a low phytanic acid diet will produce some clinical improvement, and this would suggest that, in this condition, the neurological signs are complications of the metabolic error rather than the direct manifestation of a genetic abnormality.

The fundus appearances in these cases do not conform to any pattern and the term "pigmentary degeneration of the retina" is sufficiently non-specific to be applied to all groups. In some patients typical tapeto-retinal bone-corpuscle pigmentation is described; in others the pigment is "granular" or "clumped" or "finely dusted". The distribution of these changes also varies: maximum pigmentary disturbance may be found at the posterior pole, at the equator, or in the periphery. The retinal arterioles may be attenuated, slightly narrowed, or normal. Optic atrophy is occasionally recorded and the visual fields may be affected, although they are usually intact.

The term "chronic progressive external ophthalmoplegia", which is used to denote a slowly progressing paralysis of the extraocular and levator palpebrae muscles, has been adopted in this paper because it is purely descriptive and does not involve any commitment as to aetiology. The terms "ocular myopathy" and "progressive nuclear ophthalmoplegia", the first indicating a primary disorder of muscle and the second a degenerative process involving the brain stem nuclei of the third, fourth, and sixth cranial nerves, are avoided because they do imply that the site, if not the cause, of the disease process is known. For over 50 years it was generally accepted that chronic progressive external ophthalmoplegia was the result of a degeneration of the brain stem nuclei, a theory first proposed by Möbius (1900). Kiloh and Nevin (1951), however, reappraised the earlier myopathic theory (Fuchs, 1890) and this then became the accepted view for the next two decades. Recently the criteria involved in establishing a diagnosis of myopathy have been critically reassessed and doubt has been expressed regarding the aetiology in all cases of chronic progressive external ophthalmoplegia except those in which *post mortem* examination has demonstrated beyond doubt the site of the lesion (Walton, 1961; Daroff, Solitare, Pincus, and Glaser, 1966; Rosenberg and others, 1968; Daroff, 1969).

The two investigations on which the myopathic theory largely relies are electromyography and biopsy of the extraocular muscles, but the interpretation of such data is usually equivocal so that a definitive diagnosis cannot be made on the basis of either (Rosenberg and others, 1968). The study of certain serum enzymes which are known to rise in muscular dystrophy, an established myopathic condition, has not received much attention in relation to chronic progressive external ophthalmoplegia and therefore the results of an investigation done by one of us (P.V.M.), in which the serum creatine phosphokinase levels were measured in eleven cases unassociated with pigmentary degeneration of the retina, are presented (Table II, overleaf). These cases were diagnosed according to the classification used by Liversedge (1963) and the serum creatine phosphokinase levels were measured by the method of Tanzer and Gilvarg (1959).

In the muscular dystrophies, especially of the Duchenne type, there is a marked rise in many serum enzymes, including creatine phosphokinase, aldolase, aspartate and alanine aminotransferases, and lactic dehydrogenase. The serum level of creatine phosphokinase, which is found almost exclusively in muscle, appears to be the most sensitive index for the diagnosis of muscle disease. The enzyme level may rise before the disease becomes clinically apparent and it can be used for the detection of clinically normal carriers of the abnormal gene causing muscular dystrophy (Hughes, 1963; Pennington, 1969).

In the above series (Table II), only one case, in which the most prominent feature of the presumed myopathy was laryngo-pharyngeal weakness, showed a small elevation of the serum creatine phosphokinase. In Table I, of the 23 cases with chronic progressive external ophthalmoplegia and pigmentary degeneration of the retina listed, serum enzyme studies were reported in seven cases. Only in Case 2 reported in this paper was the serum creatine phosphokinase raised, though the elevation was considerable, the serum creatine phosphokinase being 114 units/ml. compared with a normal range of 5–20 units/ml. Abnormal serum enzyme levels associated with progressive ophthalmoplegia have been recorded before. Magora and Zauberman (1969) found raised levels of serum creatine phosphokinase and aldolase in one patient of a series of six with progressive ophthalmoplegia, and Satoyoshi, Murakami, Kowa, Kinoshita, and Torii (1965) reported two patients who had a raised creatine phosphokinase level. Magora and Zauberman (1969) sug-

Table II *Serum creatine phosphokinase (CPK) in chronic progressive external ophthalmoplegia unassociated with pigmentary degeneration of the retina (normal $< 1\cdot5$)*

Case no.	*Sex*	*Age (yrs)*	*Ptosis*	*Ophthalmoplegia*	*Facial weakness*	*Limb or trunk weakness*	*Laryngopharyngeal weakness*	*Family history*	*Diagnosis*	*Serum (CPK) (u./ml.)*
1	M	75	+					+	Myopathic ptosis	0·25
2	F	38	+					+	Myopathic ptosis	0·25
3	M	61	+	+		+	+	+	Descending ocular myopathy	0·25
4	F	60	+	±				+	Ocular myopathy	0·6
5	M	69	±	+		+			Descending ocular myopathy	0·7
6	F	35	+	+	+	+	+		Descending ocular myopathy	0·7
7	F	45	+	+		+			Descending ocular myopathy	0·8
8	M	72	+	+	+		+	+	?Oculopharyngeal myopathy	1·2
9	M	55	+					+	Myopathic ptosis	1·4
10	F	53	+	+	+	+	+		Descending ocular myopathy	1·4
11	M	63	+		+		+	+	Oculopharyngeal myopathy	4·1

gested that enzyme levels were usually normal in patients with progressive ophthalmoplegia because of the small muscle bulk involved. All five cases with raised serum enzyme levels mentioned above had evidence of muscle disease outside the extraocular musculature, and this would tend to confirm the view that it is the bulk of muscle affected by disease which determines whether or not enzyme levels will rise.

The abnormal enzyme levels in cases of chronic progressive external ophthalmoplegia would appear to support the view that the disorder is myopathic in nature. It is known, however, that a modest rise in the serum level of creatine phosphokinase can occur in association with muscle denervation (Hughes, 1963; Goto, Peters, and Reese, 1967). It is stated in the latter paper that "creatine phosphokinase elevation alone cannot always distinguish between progressive muscular dystrophy and other neuromuscular disorders". Thus the detection of moderate rises in serum enzyme levels in cases of chronic progressive external ophthalmoplegia does not necessarily prove them to be myopathic, but a substantial rise, as in our Case 2, must provide strong support for a myopathic aetiology.

Summary

Two cases of progressive external ophthalmoplegia associated with pigmentary degeneration of the retina are described and the relevant literature reviewed. The value of serum enzyme studies in the diagnosis of myopathy of the extraocular muscles is discussed and a study of serum creatine phosphokinase in eleven other cases of progressive external ophthalmoplegia is reported.

Mr. P. V. Mills wishes to thank Dr. G. K. McGowan, Consultant Chemical Pathologist, Bristol Royal Infirmary, for kindly arranging the serum creatine phosphokinase estimations listed in Table II.

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Foreign bodies as a cause of conjunctival pseudomembrane formation

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There are certain pathological features common to all forms of conjunctivitis. Essentially these are the fundamental characteristics of inflammation: hyperaemia, stasis, cellular exudate, and a fibrin-rich oedematous fluid, added to the reaction of the conjunctival tissues themselves. However, when a fibrin-rich exudate is formed on the surface of the conjunctiva, a pseudomembranous conjunctivitis results. This pseudomembrane consists of a close network of fibrin including leucocytes and other exudative products. It is easily peeled off but may soon recur.

In membranous conjunctivitis, the exudate is poured onto the surface but also permeates the superficial layers of the epithelium, and it may actually penetrate the conjunctival tissue down to the tarsal plate, with some obliteration and thrombosis of vessels. Later, organization of the membrane may take place with neovascularization and fibroplasia. In pseudomembranous conjunctivitis, the exudate is more superficial and there is no organization of the fibrin matrix.

The formation of conjunctival membranes and pseudomembranes may be evoked by a variety of factors, including common bacterial organisms such as various streptococci and, less commonly, mycobacteria and actinomycetes. Viruses have also been implicated, as in epidemic keratoconjunctivitis. Other aetiological factors are allergic, as in vernal catarrh; toxic, as in erythema multiforme; and chemical irritants, such as acids and alkalis, as well as various vegetable and animal irritants (Duke-Elder, 1965).

The three following case reports exhibit a common factor which is new in our experience as a possible cause for the formation of conjunctival membranes. This factor is a foreign body, found in the membrane itself, with attendant foreign-body cellular reaction demonstrated on histopathological examination.

Case reports

Case 1, a 65-year-old white man, presented with the complaint of burning and redness in both eyes of 2 to 3 weeks' duration.

EXAMINATION

The palpebral conjunctivae were injected, with scanty mucopurulent exudate in the inferior cul-de-sacs and a few conjunctival follicles. Gram and Wright stains of conjunctival scrapings showed some polymorphonuclear cells and scattered Gram-positive cocci.

TREATMENT

The patient was placed on polymyxin-bacitracin-neomycin drops four times a day.

PROGRESS

He was seen again one week later; there was not much improvement symptomatically and no significant change on ocular examination.

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Cultures were taken with a cotton swab from the cul-de-sacs, and a KOH preparation for fungi was negative. All medication was stopped and the patient was asked to return in 5 days. At the next visit he was found to have a pseudomembrane in the left inferior cul-de-sac which was easily stripped away and was submitted for histopathological examination. A conjunctival biopsy specimen which was also submitted showed only chronic inflammatory changes.

Microscopical examination of the pseudomembrane showed numerous acute and chronic inflammatory cells. In addition, birefringent foreign bodies identified as cotton fibres were noted, together with occasional foreign-body giant cells. Special stains for fungi, bacteria, and acidfast bacilli were negative. The culture produced a moderate growth of *Staphylococcus aureus*. A topical chloramphenicol preparation was prescribed and the patient's condition subsequently improved.

Case 2, a 58-year-old white man, received a foreign body in the right eye while working with some welding slag. He did not seek medical attention immediately but a few days later noted a dry sensation and a whitish plaque in the inferior cul-de-sac.

EXAMINATION

At the clinic this membrane was easily peeled off from the conjunctiva and was submitted for histopathological study. Microscopical examination revealed an eosinophilic granular material with acute and chronic inflammatory cells. Also present was a granulomatous infiltrate with numerous foreign-body giant cells containing birefringent foreign bodies. Cultures were negative.

Case 3, a 62-year-old white woman, came to see an ophthalmologist because her left eye had been red and irritable for one week.

EXAMINATION

A tenaciously attached yellowish-grey membrane was seen upon eversion of the left upper lid (Figs 1 and 2).

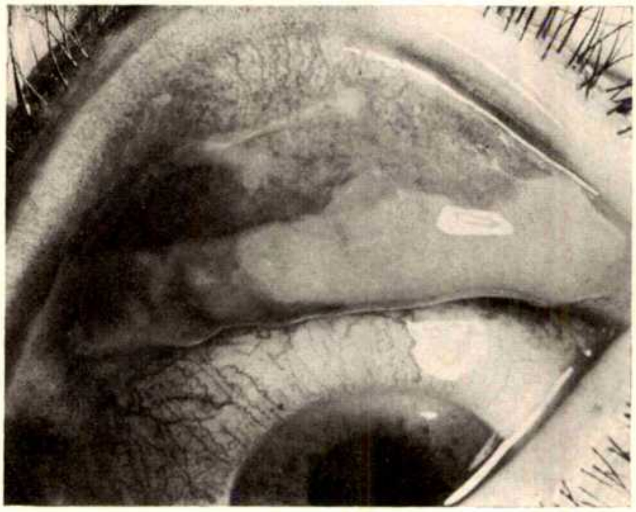

FIG. 1 *Pseudomembrane on palpebral surface of upper lid*

This was removed with some difficulty, leaving numerous bleeding sites, and was submitted to the pathology laboratory. It was found to be a pseudomembrane, consisting of an eosinophilic fibrillar matrix in which numerous acute and chronic inflammatory cells were embedded (Figs 3 to 6). Several foreign-body giant cells with birefringent foreign-body particles were noted. Special stains for bacteria and fungi were negative. Cultures revealed a moderate growth of *Staphylococcus aureus*.

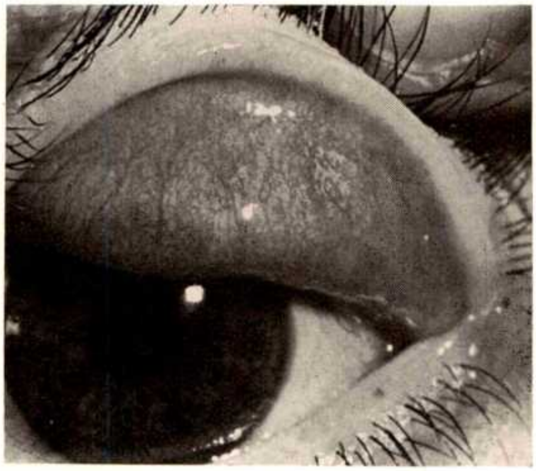

FIG. 2 *Clear palpebral surface after removal of pseudomembrane and topical administration of antibiotic for one week*

Comment

In each case, histopathological examination revealed a pseudomembrane. Under low-power magnification the specimens showed marked cellularity with no blood vessels (Fig. 3).

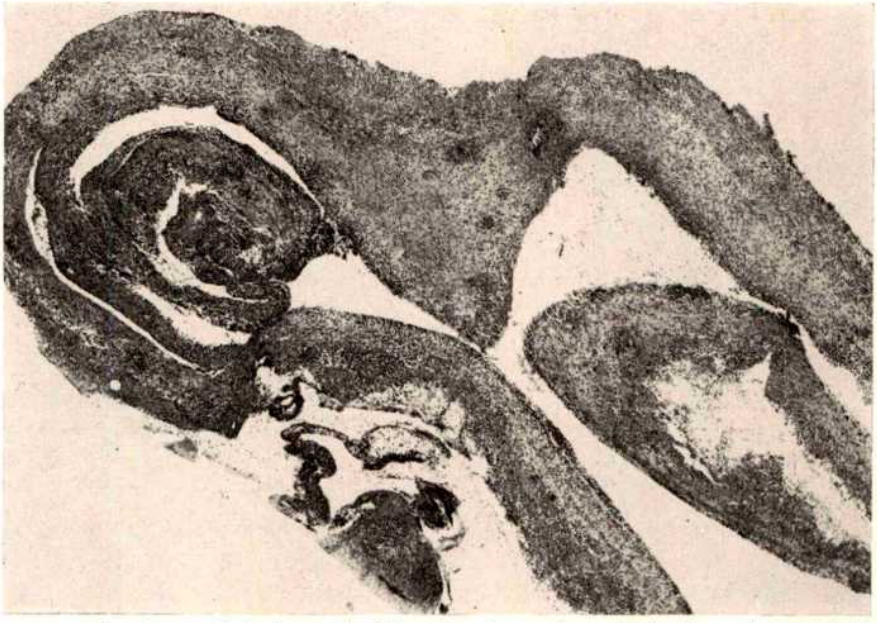

FIG. 3 *Low-power photomicrograph of pseudomembrane, demonstrating its marked cellularity and absence of blood vessels. Haematoxylin and eosin.* × 10

Higher magnification revealed many polymorphonuclear leucocytes and mononuclear inflammatory cells (Fig. 4), embedded in an acellular eosinophilic fibrillar matrix. Special stains showed this matrix to have the histochemical characteristics of fibrin (Fig. 5). In addition, numerous foreign-body giant cells containing birefringent foreign bodies could be demonstrated with partial polarized light (Fig. 6).

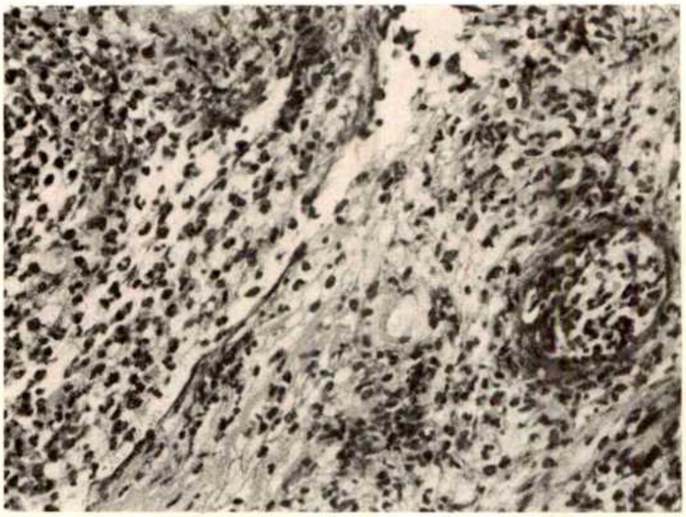

FIG. 4 *Numerous polymorphonuclear leucocytes and mononuclear inflammatory cells in a meshwork of eosinophilic fibrillar-like material. Note the large foreign-body giant cell. Haematoxylin and eosin.* ×375

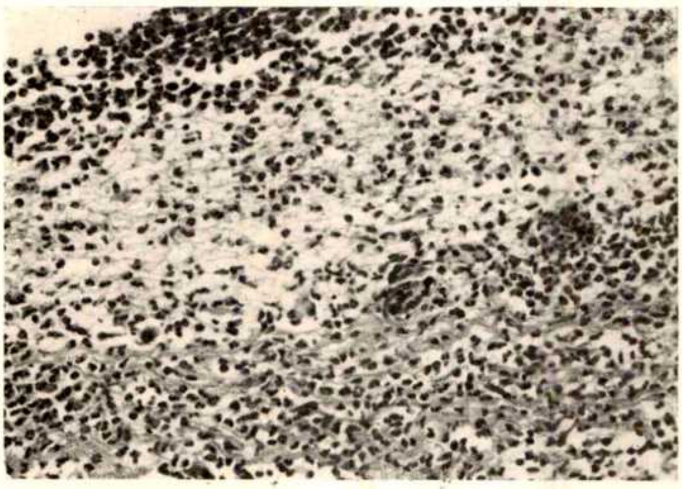

FIG. 5 *Eosinophilic fibrillar meshwork stains positive for fibrin. Mallory's phosphotungstic acid-haematxoylin.* ×260

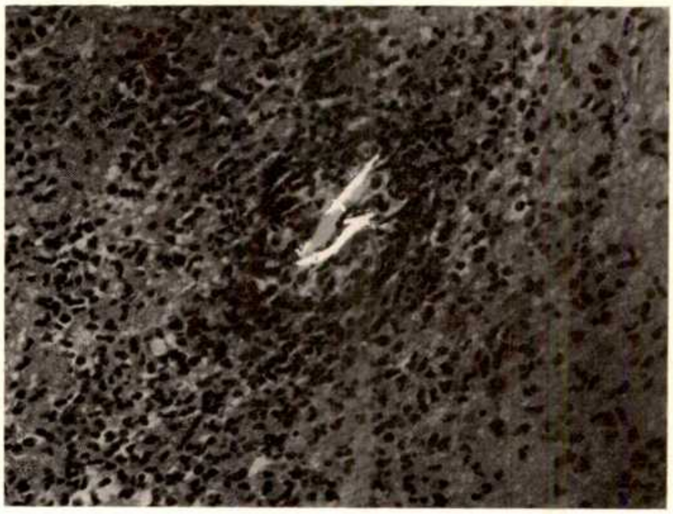

FIG. 6 *Birefringent foreign bodies embedded in a foreign-body giant cell demonstrated with partial polarized light. Haematoxylin and eosin.* ×375

The question arises as to the relevance of these findings in view of the positive *Staphylococcus aureus* cultures. These organisms are among the commoner causes of conjunctival membranes. However, four points support the thesis that foreign bodies can either directly cause conjunctival pseudomembrane formation or act as inciting agents superimposed upon underlying pathogens:

(1) There are innumerable cases of conjunctivitis due to *Staphylococcus aureus* that do not form any membrane.

(2) No membrane was found in Case 1 until after a cotton swab was applied to the conjunctiva, and then the foreign bodies were identified microscopically as cotton fibres.

(3) Cultures for pathogens were negative in Case 2.

(4) All three cases clearly demonstrated the common factor of numerous foreign-body giant cells surrounding birefringent foreign bodies.

The final histological diagnosis of all three specimens was pseudomembrane of the conjunctiva secondary to foreign bodies.

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Unusual presentation of ocular *Toxocara* infestation

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Since Wilder (1950) first demonstrated the presence of nematode larvae (subsequently identified as second-stage larvae of *Toxocara canis*) in a number of eyes enucleated for suspected retinoblastoma, the possibility that such infestation may be the aetiological factor in certain cases of uveitis and endophthalmitis has been well recognized. Many reports of such infestation proven by identification of the worm in serial sections have now appeared in the literature, but the mode of presentation of the case to be described appears sufficiently unusual to be worth reporting.

Case report

The mother of the patient, a 3-year-old girl, gave the history that for the previous 10 days the child's right eye had appeared injected and mildly irritable. The onset of the inflammation coincided with an apparent attack of shingles over the area of the left fourth thoracic dermatome, and 24 hours before the ophthalmological consultation the mother had noted a white spot on the lower portion of the right iris and this had gradually increased in size.

The child had been subject to recurrent middle ear infections for the past year, and seemed to suffer from more than the usual number of coughs and colds. In the light of subsequent findings, particular enquiry was made concerning contact with dogs, but the family had never owned a dog and their home environment was such that contact with areas contaminated by dogs appeared unlikely.

Examination

The eye showed very slight conjunctival injection and a 3 mm. hypopyon was present. There was a one-plus aqueous flare and the anterior chamber showed a number of circulating cells which appeared large and slightly pigmented. A thin fibrinous exudate occluded the pupil, but full pupillary dilation was attained quite easily and binocular indirect ophthalmoscopy revealed no fundus pathology other than a small white punched-out area adjacent to the upper temporal vessels anterior to the equator; this area appeared quite inactive.

Treatment

Topical prednisolone and atropine was given and 2 days later the hypopyon had completely cleared although there were still some circulating cells. An excellent view of the whole of the periphery of the fundus as far forward as the ora serrata could now be obtained and no other pathology could be seen.

Routine investigations, including physical examination, chest *x* ray, and full blood examination were normal, with the exception that the blood eosinophil count was 4 per cent.; in the light of subsequent events, this was probably of significance.

Progress

Over the next few weeks the cells in the anterior chamber cleared and the eye whitened. However, 4 weeks after the initial presentation, fundus examination revealed a yellowish-white mass at the ora

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serrata in the upper temporal quadrant. This mass was approximately four disc diameters in size and appeared raised, with several irregular flocculent strands radiating from it into the vitreous. Examination under anaesthesia confirmed these findings, and also confirmed the presence of the inactive punched-out lesion previously described. The remainder of the examination of the involved eye and of the fellow-eye was normal. *X* rays of the eye showed no calcification. The child was seen by three other ophthalmologists in consultation; it was considered that, although there was some possibility that the appearances were due to nematode infestation or other pathology, the presence of retinoblastoma could not be excluded. It was also considered that the situation of the mass and the possibility that it might be part of a diffuse infiltrating retinoblastoma were a contraindication to radiotherapy.

The eye was therefore enucleated.

At the time of the examination there was no specific test for *Toxocara* immediately available in Australia, but Dr. C. Dobson of the Department of Parasitology, University of Queensland, has examined the patient's serum against *Toxocara canis* and other helminths, using passive reversed Arthus and passive cutaneous anaphylaxis tests in guinea-pigs. He reported the test positive to *Toxocara canis* only, although the test was much weaker than other positive sera and the control from the dog (the test was performed 5 months after enucleation).

Pathology (Figs 1 and 2)

MACROSCOPIC APPEARANCES

The cornea is clear. Horizontal opening section above the disc. The retina is in place and the disc and macula are somewhat prominent. There is a greyish-white localized thickening of the retina at the ora serrata on the temporal side astride the horizontal meridian. From this thickening, thin strands like threads of cotton-wool radiate into the vitreous and over the pars plana. The vitreous is otherwise clear and gelatinous except for a few small clumps of cells. The lens is clear. There is some retinal detachment, which transilluminates, inferior to the focus at the ora serrata.

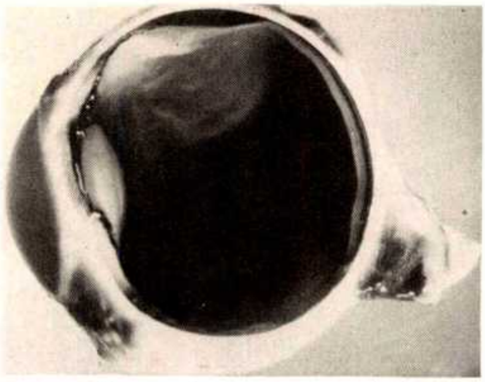

FIG. 1 *Macroscopic appearance on sagittal section, showing anterior fundus lesion*

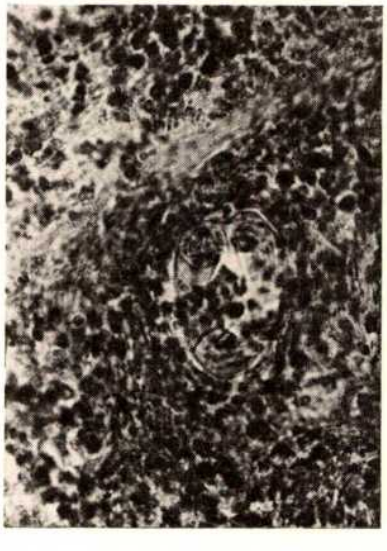

FIG. 2 *Microscopic appearance, showing segment of organism.* ×270

SECTIONS

These show a localized granulomatous inflammatory reaction at the ora serrata involving the vitreous, retina, and ciliary epithelium. The reaction has broken through the ciliary epithelium into the stromal tissue of the pars plana and anterior choroid. The granuloma consists of fibrin, lymphocytes, epithelioid cells, foreign body giant cells, and innumerable eosinophils.

In two of the 165 serial sections through the granuloma, part of a nematode larva is present lying coiled among the inflammatory cells. The larva is 18 μ in diameter and approximately 250 μ in length. Where it is cut in transverse section, the following features can be recognized – a refractile cuticle with lateral spines or alae and two granular excretory columns. Where the larva is cut longitudinally, small body nuclei can be discerned arranged in rows on either side of a central tube. No mouth parts can be identified.

Mononuclear cells and eosinophils have migrated from the granulomatous focus into the vitreous. There is an inflammatory infiltration of the iris and trabecular meshwork by plasma cells and eosinophils and a few small keratic precipitates. The temporal choroid is focally infiltrated by lymphocytes and eosinophils. The retina is thickened by oedema, especially at the macula, and there is lymphocytic infiltration of the walls of the retinal blood vessels.

DIAGNOSIS

Nematode endophthalmitis (*Toxocara canis* larval infestation).

The sections were also examined by Professor J. F. A. Sprent of the University of Queensland who confirmed the diagnosis of *Toxocara canis*.

Comment

This case of ocular *Toxocara canis* infestation was of interest in that the presentation was in the nature of an acute anterior uveitis with hypopyon with subsequent development of a retinal mass. The more usual method of presentation appears to be either as a chronic uveitis or endophthalmitis often with associated retinal detachment or as a solitary retinal granuloma at the posterior pole (Duguid, 1961a, b). In Duguid's series of cases a discrete lesion was not seen in the peripheral fundus other than in cases of chronic endophthalmitis with retinal detachment. Hogan, Kimura, and O'Connor (1965), discussing peripheral retinitis and chronic cyclitis in children, felt that some of their cases might have been due to nematode infestation but they described no specific diagnostic features in these cases.

Perkins (1966) reported a number of cases of peripheral choroiditis in children thought to be possibly due to *Toxocara;* the diagnosis was based on blood eosinophil count, a positive skin-test to *Toxocara* antigen, and a history of contact with dogs, but none of these eyes was removed and sectioned. Perkins felt that *Toxocara* infestation was a probable or possible cause of the uveitis in 10 per cent. of his series. He mentioned one case of acute anterior uveitis with a hypopyon and raised blood eosinophil count but gave no further details.

When the child presented no test was immediately available in Australia which might have been helpful in diagnosing *Toxocara canis* infestation, and because of the hypopyon with large cells in the anterior chamber and the subsequent appearance of a peripheral retinal mass it was considered that the condition might represent a diffuse infiltrating retinoblastoma as described by Schofield (1960). The possibility of retinoblastoma was also enhanced by the report of Howard and Ellsworth (1966) that, in their series of retinoblastomata, 26 per cent. of eyes showed the sole or major growth of tumour in the periphery. In retrospect it is probable that anterior chamber aspiration and examination of the aspirate would have helped in the diagnosis. The fact the that hypopyon cleared rapidly with topical steroids is also in keeping with the basically inflammatory nature of the disease. When the mass in the fundus became evident, a subconjunctival injection of depot corticosteroids as described by Nolan (1968) would possibly have been helpful as a diagnostic measure, as a retinoblastoma would not be expected to show any significant change following this treatment.

Summary

A case of ocular *Toxocara canis* infestation presenting as an acute uveitis with hypopyon is reported. The eye was enucleated after the development of an anterior retinal mass which was thought to be a retinoblastoma. Serial sections of the mass revealed the presence of a *Toxocara canis* larva.

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Role of penetrating grafts in herpetic keratitis

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Leigh (1966) stated that "at the present time possibly no corneal disease presents a wider variety of problems for keratoplasty than herpetic keratitis in all its forms". These problems involve the difficulty of handling friable waterlogged tissues, the decision whether to use a lamellar or full-thickness graft, the timing of the graft, and the ability to maintain a clear graft postoperatively. Nevertheless there is general agreement that keratoplasty is of value in cases of herpes simplex keratitis. Therapeutic keratoplasty is used for extensive recurrent dendritic ulceration, for spreading stromal herpes, and to remove chronically infected tissues by means of lamellar grafts. Tectonically grafts are used in herpetic keratitis in cases of perforation or threatened perforation of the cornea. Finally, opacified and quiescent cornea may be treated by optical penetrating grafts. It is felt that the dangers of penetrating keratoplasty are exaggerated and that in fact penetrating grafts produce less complications and difficulties and give better long-term results than lamellar grafts. With these points in mind a simpler direct approach has been made to this problem of herpetic keratitis in a series of sixteen cases (Table, overleaf):

(1) Penetrating grafts were used in all cases.

(2) With the exception of corneae with descemetocoeles or perforations, all grafting was carried out on clinically quiet eyes.

(3) Corticosteroids were administered in the same pattern in all cases irrespective of herpetic activity or vascularization.

(4) All donor corneae were removed and grafted to the host within 12 hours of the death of the donor.

Method

Bacteriological cultures from the donor eyes are considered unnecessary and time wasting. In the time from their removal from the donor to the operation (*maximum 12 hours*) the eyes are stored in sterile liquid paraffin at 4°C. The eyes are removed from their containers and washed thoroughly in sterile saline to remove all traces of liquid paraffin. A 7 or 8 mm. trephine removes a full-thickness disc of donor cornea and the *same* trephine is used to remove a full-thickness disc from the affected patient's eye under general anaesthesia. In all cases the positioning of the trephine on the patient's cornea is such as to remove the maximum amount of affected tissue, and in attempting to achieve this the position of corneal vessels is ignored.

Direct edge-to-edge suturing is carried out using 7/0 black silk – a procedure facilitated by the use of the operating microscope. The number of sutures required, depending on the need to achieve an airtight wound, varied from twelve to sixteen. Air is introduced into anterior chamber *via* the wound at the end of the operation and this is followed by the subconjunctival injection of 12·5 mg. prednisolone and the local instillation of chloramphenicol drops. A single pad covers the eye.

The first dressing is carried out after 24 hours, and atropine and chloramphenicol drops are instilled once daily. The patient is mobilized at this time. From the fifth postoperative day local

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Table *Results in sixteen cases*

Case no.	Age (yrs)	Sex	Description before graft	Duration (yrs)	Visual acuity		Observation period (yrs)	Remarks
					Preoperative	Post-operative		
1	28	M	Corneal scarring centrally in anterior stroma after disciform keratitis Hypoaesthesia over scarred area No vessels	2	Counting fingers	6/9	2	Graft clear Steroid drops tailed off after one year
2	54	M	Central corneal leucoma to posterior third of stroma with vascularization one quadrant Surrounding clear corneal tissue	10	Counting fingers	6/18	1½	Graft clear Free of vessels Local steroids continued
3	24	M	Perforated central necrotic ulcer after local steroid administration 9 years previous history of stromal keratitis with marked uveitis Superficial corneal vascularization	9	Perception of light	6/9	3	Graft clear Conjunctival flap fashioned to cover perforation on admission Penetrating graft 3 weeks later Local steroids continued for 2 years
4	42	M	Ruptured descemetocoele after recurrent stromal herpes	5	Hand movements	6/6	5	Graft clear Patient wearing contact lens 4 years postoperatively oedema of graft appeared Steroid drops increased Dendritic ulcer developed at periphery of graft; iodized Steroids continued throughout
5	68	F	Necrotic thinned central cornea Marked deep vessels approaching from one quadrant after recurrent dendritic ulceration	10	Counting fingers	6/60	2	Graft clear Lens opacities present Dendritic ulceration 6 months postoperatively Steroids stopped, ulcer iodized Graft oedema appeared; steroids recommenced 14 months postoperatively dendritic ulceration reappeared, iodized but steroids not stopped
6	50	M	Deep excavated central ulcer crater Arborizing deep vessels supplied by single feeder vessel after recurrent dendritic ulceration	5	Counting fingers	6/18	½	Graft clear Retrocorneal membrane formed off axis Local steroids still given
7	38	M	Localized central corneal leucoma with deep vessels after recurrent dendritic ulceration	18	6/60	6/9	1½	Graft clear Local steroids still given

8	53	M	Thickened oedematous cornea after recurrent dendritic ulceration on previous penetrating graft for herpes keratitis	17	Counting fingers	6/12+	1½	Graft clear Dendritic ulcer developed on 1st penetrating graft 2 months postoperatively Iodized and steroids continued to maintain clarity of graft Ulcer healed to give stromal scarring necessitating second graft Second graft clear Steroids instilled continuously
9	63	M	Deep stromal opacification with marked deep vascularization and overlying oedema	4	3/60	Perception of light	2	Sutures removed at 3 weeks Graft tilted necessitating second graft which developed dendritic ulceration with glaucoma Steroids stopped Complete opacification of graft
10	28	F	Diffuse stromal keratitis with irregular corneal surface No epithelial activity Extensive deep vessels	5	Counting fingers	6/12	2	Graft clear Widespread corneal oedema developed 7 months postoperatively on reducing local steroids Visual acuity reduced to hand movements Steroids restarted at 2-hrly frequency Oedema commenced to clear in 48 hours Steroids continued
11	22	M	Thinned ectatic cornea with deep and superficial vessels in leucomatous area centrally	9	Perception of light	Hand movements	9	Graft clear Penetrating graft 4 years previously Cataract and posterior synechiae present preoperatively
12	36	M	Recurrent dendritic keratitis in and around previous lamellar graft carried out 16 years previously	1	Counting fingers	6/6	1	Graft clear Steroid drops stopped after 9 months
13	43	F	Disciform keratitis with recurrent flare-ups, associated uveitis, and dendritic ulceration Deep vessels limited to small sector	12	Hand movements	6/9	1½	Graft clear Steroids still continued
14	41	M	Stromal keratitis with deep vessels and overlying oedema surrounding rim of clear cornea	3 mths	Perception of light	6/12	1	Graft clear At 3 and 10 mths in postoperative period, fine widespread oedema developed with fine deep vessels in graft when patient stopped steroids Admission and intensive local steroids cleared graft on each occasion with retraction of vessels
15	22	M	Central corneal nebula extending to deep stroma associated with deep vessels in one quadrant	16 mths	Hand movements	6/6	5 mths	Graft clear Deep vessels skirting graft junction Local steroids continued
16	52	M	Recurrent disciform keratitis Free from corneal vascularization	2	6/36	6/9	2	Graft clear Local steroids continued for 9 months

steroid drops are instilled four times daily; the antibiotic drops are continued until the tenth postoperative day and then stopped.

Alternate sutures are removed under local anaesthesia 4 weeks after the operation and the remaining sutures at 6 weeks. During this postoperative period atropine 1 per cent. and steroid drops four times daily are continued. In all cases local steroids were used for a minimum of 4 months and only then tailed off to twice daily instillation during the following 3 months and finally to zero in the next 2 months. However, special note was made, with regard to steroid administration, of those cases which showed marked vascularization at the time of operation or in which a large amount of affected tissue was left in the host cornea. The amount of steroid administration in these cases is directly related to the amount of vascularization. If any of these grafts developed signs of vascularization or oedema, drops were increased to 2-hrly instillations and the patient was re-admitted to hospital. The oedema and vascularization is reversible in these cases and steroids are then continued indefinitely thereafter. Thus, with the exception of this type of case, steroids are administered locally from the time of the operation for a period of 9 months.

Discussion

It has been stated (Hogan, 1958; Leigh, 1966) that penetrating keratoplasty carries well-recognized complications which include failure of re-formation of the anterior chamber, iris prolapse, formation of anterior synechiae, development of glaucoma, and dislocation of the graft. In our experience with other penetrating grafts, supported by the results of this relatively small series, these complications should not occur. Indeed, with the exception of Case 9 in which the sutures were removed prematurely, none of the so-called well-recognized complications occurred, which supports our original decision to carry out penetrating keratoplasties on all these cases. Furthermore, it is felt that the technical difficulty in dissecting and suturing a lamellar graft outweighs its claimed main advantage of safety and that only in rare cases with superficial herpetic lesions does a satisfactory optical result occur.

The timing of the grafts presented no problem since they were carried out on clinically "quiet" eyes which for the purposes of this series meant the relative reduction of ciliary and conjunctival injection, an anterior chamber free of flare and cells, and a cornea where an attempt at epithelialization was being made. These findings, in conjunction with freedom from any marked pain, photophobia, or lacrimation, completed the picture. The time taken to achieve the quietened eye before perforating keratoplasty varied in each case but was never less than 2 months; some cases required a tarsorrhaphy to aid the healing processes. An exception to this waiting rule was made in Cases 3 and 4 in which perforation had occurred.

The pattern of steroid administration both in frequency and duration has produced very satisfactory results in maintaining graft clarity. It appears that continued use of local steroids is necessary for at least 9 months even in the face of frank dendritic ulceration which, if it appears, is treated by iodization – the results of which are demonstrated by Cases 4, 5, and 8. The other important point is that in cases with deep vascularization at the time of operation, or in which a large amount of affected host cornea remains, the frequency of local steroid administration must be increased if vascular invasion threatens the graft. Despite the sustained local steroid administration, retardation of wound healing and glaucoma have not presented any problems in the series.

The chief complications were:

(*a*) *At operation* None. No attempt was made to reduce the vascularization preoperatively, except by the use of local steriods. Any bleeding from vessels at operation was ignored.

(*b*) *Vascularization surrounding the graft* When this appeared in the early postoperative stages its extension was controlled by increasing local steroids.

(*c*) *Oedema of the graft* This was generally related to the amount of vascularization present before grafting. It is always a danger even as late as 3 or 4 years after the operation.

(*d*) *Recurrence of dendritic ulceration* This was treated routinely by iodization, but steroid therapy had to be continued to maintain clarity of the graft.

In a very large general hospital with a high percentage of geriatric patients a supply of donor material is readily available to enable grafting as soon as possible after the death of the donor – how important a part this played in the production of these very satisfactory results is difficult to determine. The only other point to be made in this series is the fact that younger patients tended to produce a better result.

Conclusions

In this series of cases the decision to carry out corneal grafting was made on the grounds that there had been a loss of visual acuity below 6/18 with the eye in the quiet state. The exceptions were the cases of corneal perforation. Neither the visual acuity of the unaffected eye nor the degree of vascularization in the affected eye influenced the decision to operate.

Penetrating keratoplasty is a straightforward procedure from the purely technical point of view and is devoid of operative complications.

Steroids are required to maintain the clarity of the graft. An increased frequency of administration is required in proportion to the amount of vascularization at the time of operation and in cases in which a large amount of diseased host corneal tissue is left behind after grafting.

With the exception of Case 9 there has been total success in maintaining graft clarity using this approach, a fact which becomes more significant when it is remembered that four cases (4, 5, 8, and 9) in this series had suffered a bout of dendritic ulceration in the postoperative period.

Summary

Results are presented of adopting a simple approach to grafting in sixteen cases of herpetic keratitis. Penetrating grafts were carried out in all patients and local steroids were used in the postoperative period.

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Therapeutic keratoplasty in *Pseudomonas pyocyaneus* corneal ulcers

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Sloughing virulent corneal ulcers are still very common in India. Even with the best medication they often fail to respond and in such cases the eyes are invariably lost. This is especially true in the case of ulcers caused by *Pseudomonas pyocyaneus*, when the clinical course is so fulminating that only a bold and timely decision can save the eye. Keratoplasty has been found to be a potent eye-saving procedure in 36 apparently hopeless cases of sloughing hypopyon corneal ulcer due to this organism seen in the corneal surgery unit in the years 1964 to 1969.

Material and methods

Surgery was necessitated in these 36 cases for the following reasons: failure of medical treatment (10), perforated cornea (5), impending perforation (17), totally sloughed off cornea (4). The ages of the 36 patients ranged from 10 to 60 years. In 32 there was defective projection of light. Written consent for evisceration had been obtained before surgery, but it was decided that grafting could be performed instead.

TECHNIQUE

The method of cutting the graft varied according to the condition of the cornea.

(a) Cases without corneal perforation

The corneal trephine of appropriate diameter was adjusted to 0·5 mm. depth and a deep groove was made in the cornea. A deep lamellar dissection was started and, if all infected tissue could be removed, a lamellar graft was applied. No attempt was made to drain the hypopyon.

In cases in which the graft bed was found to be involved after a deep lamellar dissection, penetrating keratoplasty was carried out. The anterior chamber was opened with the tip of a von Graefe cataract knife through the trephined groove. The button was cut away along the trephine mark by enlarging the puncture with the help of Castroviejo's corneal scissors.

(b) Cases with corneal perforation

A trephine groove of required size was made in the cornea to outline the part required for excision. The blades of Castroviejo's corneal scissors were introduced through the perforation and taken radially to the edge of the groove in the host cornea. The cornea was excised along the line of the trephined groove.

Homografts were used in all cases, fresh donor tissue in 29 cases and glycerol-preserved tissue in seven.

SURGERY (Figs 1 to 4)

The operations were performed under general anaesthesia. The intraocular pressure was kept low by intravenous mannitol in thirty cases and by intravenous acetazolamide in six. For penetrating

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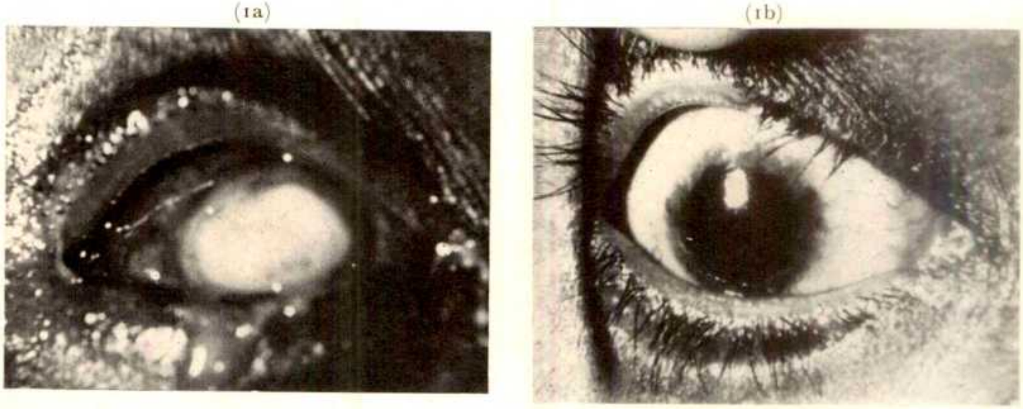

FIG. 1 (a) *Preoperative appearance of sloughing* Pseudomonas pyocyaneus *corneal ulcer*

FIG. 1 (b) *Postoperative appearance, showing transparent graft after a* 10 *mm. penetrating keratoplasty*

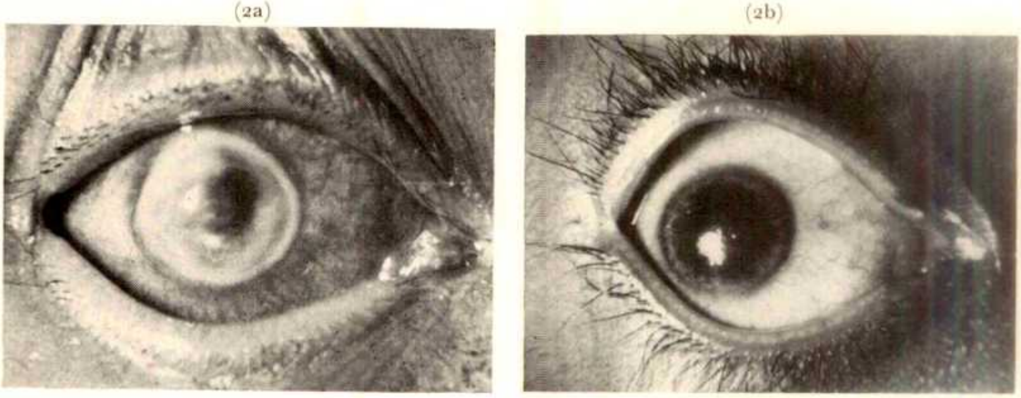

FIG. 2 (a) *Appearance of total descemetocele with slough on borders*

FIG. 2 (b) *Clear* 10 *mm. lamellar graft*

grafts four peripheral iridectomies were performed, one in each quadrant. The anterior chamber was flushed continuously with sterile normal saline containing framycetin (0·5 ml. in 20 ml. distilled water). Corneal sutures with 8–0 virgin silk were placed 1·5 mm. apart to make the wound air-tight. In suturing, the bite in the recipient side should be 1·5–2 mm. so that the needle does not cut through the oedematous edges.

POSTOPERATIVE PROCEDURE

A binocular bandage was applied for 24 hrs in lamellar grafts and 6 days in penetrating grafts.

Postoperative intravenous injections of 275 mg. pyrolidinomethyl tetracycline were given 6-hrly for 10 days. The patients also received acetazolamide 250 mg. 8-hrly, vitamin C 1 g. daily, and vitamin A 50,000 units daily. Framycetin eye ointment was applied daily, and neosporin and atropine ointment 1 per cent. were applied for 1 month. The sutures were removed on the 21st postoperative day.

Observations

(A) LAMELLAR KERATOPLASTY (Tables I and III)

In eight cases, including two cases of descemetocele, the necrotic tissue could be removed by deep lamellar dissection almost up to Descemet's membrane with an 8- or 11-mm. graft (Table 1). A slight leak of aqueous occurred in one case. Seven of these eight cases had defective projection of light.

Table I *Result of lamellar keratoplasty in* Pseudomonas pyocyaneus *corneal ulcers (8 cases)*

Size of graft (mm.)	*Total no. of cases*	*Initial faulty projection of light*	*Postoperative complications*			*Reinfection with loss of eye*	*Final visual acuity*			
			Iritis	*Punctate dots in graft bed*	*Epithelial ulcer*		6/60	6/36	6/24	6/18
8	3	2	3	3	3	–	–	–	2	1
11	5	5	5	5	5	1	2	1	–	1

POSTOPERATIVE COMPLICATIONS (Table I)

Iritis was controlled by medical treatment in all cases.

The small punctate dots noted in the bed of the graft were due to residual infection. This was controlled by the frequent local instillation of framycetin eye drops in the immediate postoperative period in addition to the systemic medication.

Uncontrolled severe infection occurred in one case and the eye was lost although a total keratoplasty was performed on the second day.

Epithelial ulceration appeared in the 2nd and 3rd postoperative week in all eight cases; this healed in 1 to 2 weeks, but in one case lateral tarsorraphy was required.

(B) PENETRATING KERATOPLASTY (Tables II and III)

In 28 cases penetrating keratoplasty was performed as the infection had spread deep into the cornea or had caused perforation. In 25 cases there was defective projection of light. Four eyes were lost, three because of uncontrolled severe infection and one because of secondary glaucoma. In the seven cases in which preserved corneal tissue was used, the optical results were inferior to those in which fresh material was used.

Table II *Result of penetrating keratoplasty in* Pseudomonas pyocyaneus *corneal ulcers (28 cases)*

Donor tissue	*Size of graft (mm.)*	*Total no. of cases*	*Initial faulty projection of light*	*Postoperative complications*				*Reinfection*	*Epithelial ulcer*	*Final visual acuity*			
				Iritis	*Anterior synechiae*	*Glaucoma*	*Cataract*			< 6/60	6/60	6/18	6/12
Fresh	8	7	4	7	4	–	–	–	1	3	–	4	–
	9	3	3	3	1	1	1	–	–	3	–	–	–
	10	5	5	5	3	–	–	–	5	1	4	–	–
	11	6	6	6	2	–	1	–	6	2	1	2	1
Glycerol-preserved	10	1	1	1	–	–	–	1	1	–	–	–	–
	11	6	6	6	–	–	–	2	6	4	–	–	–

POSTOPERATIVE COMPLICATIONS (Table II)

The mild to moderate iritis seen in all cases was controlled by medical treatment.

Anterior synechiae were observed in ten cases and anterior synechiotomy was carried out in six cases during the third postoperative week.

Epithelial ulceration occurred in twenty cases. One out of ten cases with small grafts and all eighteen cases with grafts of 10 or 11 mm. developed epithelial ulcers. Seventeen cases improved with medical treatment, and the other three healed with lateral tarsorraphy.

Table III *Final result of keratoplasty in* Pseudomonas pyocyaneus *corneal ulcers*

Types of keratoplasty	*Total no. of cases*	*Structural improvement*	*Eye lost*	*Final visual acuity*					
				6/12	6/18	6/24	6/36	6/60	<6/60
Lamellar No.	8	7	1	–	2	2	1	2	–
Per cent.	100	87·5	12·5	–	25	25	12·5	25	–
Penetrating No.	28	24	4	1	6	–	–	5	12
Per cent.	100	85·7	14·3	3·57	21·42	–	–	17·8	42·9

Discussion

Pseudomonas pyocyaneus is probably the most virulent organism causing sloughing corneal ulcers and is often responsible for panophthalmitis. It is found in the gastrointestinal tract and is a common contaminant of fluorescein solutions, so that some cases result from the use of contaminated solutions when removing corneal foreign bodies. Streptomycin, polymyxin B, Colestin, framycetin, and some of the newer broad-spectrum antibiotics may be helpful in some cases if used promptly and vigorously.

Unfortunately most of these cases come to us late after they have developed faulty projection of light or corneal perforation. It is well known that defective projection of light is a sign of impending panophthalmitis in cases of sloughing corneal ulcer, and such eyes have previously been eviscerated, though the lens and vitreous were afterwards found to be healthy.

Sporadic reports of the use of lamellar keratoplasty in such cases have been found in the literature (Coppez, 1949; Paufique, 1950; Molnar, 1960; Ricci, 1964; Stein and Lazar, 1964). Gallenga (1950) achieved structural improvement in all his eight cases and visual improvement in four.

Seven out of eight eyes in our series were saved by lamellar keratoplasty, and although improvement in visual acuity was hardly expected it was achieved in seven cases in which the final result was 6/18 to 6/60.

There are only a few reports of penetrating keratoplasty. Löhlein (1950) saved twelve out of thirteen eyes. Paufique and Philps (1950) achieved a visual acuity 6/9 in one early case, and Ricci (1964) and Hallerman (1967) also had structural successes.

In the present series, 85·7 per cent. of eyes were saved which otherwise would have been eviscerated, and the final acuity ranged from 6/60 to 6/12 in 39·2 per cent. of cases (Table III).

It is surprising that these corneal ulcers showed such a good response even with large penetrating grafts. Many surgeons fear that the infection will spread and become virulent if the anterior chamber is opened, but we found that the infective process was halted. This may occur for a number of reasons, such as the removal of infected tissue and its replacement by fresh tissue resistant to infection and the antibacterial properties of fresh aqueous.

The complications were unexpectedly few. The incidence of secondary glaucoma was low, probably because of the multiple iridectomies. The incidence of anterior synechiae was not as high as seen in optical grafts of more than 8 mm., probably because of the adherence of the iris to the anterior surface of the lens.

Summary

Therapeutic keratoplasty (8 lamellar and 28 penetrating) was performed in 36 apparently hopeless cases of *Pseudomonas pyocyaneus* corneal ulcers. The surgical procedure, post-operative complications, and structural and visual results are described.

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Retinal detachment treated with encircling silastic sponge

Further experience

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This technique, which has already been described in detail (Chawla, 1970), was used on two aphakic eyes which had already undergone unsuccessful surgery for retinal detachment and had shown early signs of preretinal retraction.

Briefly, a 7 mm. silastic sponge is halved lengthwise to produce a broad shallow implant. Monitored cryopexy is applied to the retinal tears and any suspect areas. Subretinal fluid is released as completely as possible through a meridional scratch incision, the sponge is sutured circumferentially with 5/0 Ethiflex (Ethicon No. Special 135/70) on a micro-point spatulated 8mm. half-circle needle, and its ends are secured with a clove-hitch ligature. Any extra reaction required can be produced with the light coagulator.

Since the first two cases were reported, several patients have presented with retinal detachments in which particular features called for a special approach, and this procedure has now been employed in twelve cases (13 eyes). (See Table, overleaf).

All patients were examined with the binocular indirect ophthalmoscope, a +30 D aspheric lens, and scleral depression, and all were treated with the same basic procedure described above. Manoeuvres peculiar to each case are noted in the following case reports. In all but Case 3 the retinae have remained flat and useful vision has been retained. The minimum follow-up period to date is 6 months.

Case reports

CASES 1 and 2

These have already been discussed in detail in the first paper (Chawla, 1970).

CASE 3

This girl suffered an intralenticular foreign body in August, 1969. Subsequent lens extraction was complicated by enormous vitreous loss, and shortly afterwards she developed a bullous inferior retinal detachment with an infero-nasal linear tear. There were fixed folds and a severe anterior uveitis. The left eye was normal.

Treatment

The retina did not settle with rest in bed. At operation initially, subretinal fluid was released at the 6.30 o'clock position to make sure there were no further tears, but the fixed folds prevented the retina from flattening. Monitored cryopexy was applied to the torn area and scleral buckling was carried out with a circumferential strip of 5 mm. silastic sponge and a No. 40 encircling band. The

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Table *Clinical features of twelve cases of retinal detachment*

Case No.	*Age (yrs)*	*Sex*	*Refraction*	*Preoperative visual acuity*	*Operation date*
1	53	M	+5 D sph., +1·5 D cyl., axis 80°	6/36 N8	Dec. 1969
2	48	F	+5 D sph., +1 D cyl., axis 80°	6/24 N10	Jan. 1970
3	21	F	+13 D sph., +1 D cyl., axis 90°	Counting fingers	Jan. 1970
4	77	F	+3·25 D sph., −0·5 D cyl., axis 180°	Hand movements	Jan. 1970
5	43	F	−20 D sph.	Hand movements	Apr. 1970
6†	16	M	+13 D sph.	6/60 N24	May 1970
7	45	F	−16 D sph. +1·5 D cyl., axis 90°	Bare perception of light	May 1970
8	61	F	+3·25 D sph.	6/9 N5	Jun. 1970.
9	46	F	−15 D sph.	6/36 N10	Jul. 1970
10	68	M	+11 D sph.	Hand movements	Jul. 1970
11	53	F	R. −6 D sph., −4 D cyl., axis 40° L. −6 D sph., −4 D cyl., axis 140°	Hand movements Hand movements	Jul. 1970
12	21	M	Emmetropic	6/60 N48	Jul. 1970

*RD = Retinal detachment † See Addendum

ype of retinal detachment	*Special features*	*Postoperative visual acuity*
ower RD* lacular involvement phakic revious Arruga string ixed folds and tear astride string at 5 o'clock	Vitreous loss ++ at lens extraction	6/24 N8
ower half RD extending up nasal side phakic revious Arruga string ixed folds and tear astride string at 10 o'clock	Bilateral intraocular pressure ~40 mm.Hg	6/24 N8
otal RD phakic previous procedures nferior retro-oral round tears	Intraocular foreign body April, 1969 Lens extraction with vitreous loss	No perception of light
ower RD involving macula horseshoe tears with taut opercula at 3 and 4 o'clock	Nuclear sclerosis +	6/24 N10
otal RD osterior staphyloma ultiple equatorial tears	Amblyopic eye Previous squint surgery	Counting fingers +
nferior half RD involving macula ixed folds and lower equatorial tear	Congenital cataracts Repeated needlings Nystagmus	6/24 N10
otal RD iant dialysis arge equatorial round tear	Retinal flap hanging over disc and macula	6/60 N48
emporal RD arge equatorial horseshoe tear at 2.30 o'clock	Old scleritis Marked scleral thinning	6/18+ N10
ower half and temporal RD ultiple round retro-oral tears	Subluxated lens Nuclear sclerosis ++ Only eye	6/24 N5
lmost total RD ixed folds and equatorial tears	Extracapsular lens extraction 5 needlings	6/60 N48
ilateral lower 2/3 balloon RD involving macula arge inferior temporal dialyses and much retro-oral hinning	Pigmentary glaucoma	R. 6/18 N6 L. 6/36 N24
xtensive vitreous haemorrhage nferior half RD secondary to scleral rupture	Late subluxation of lens forwards	6/36 N24 with −8 D sph.

operation, and a further similar one, failed to contain the detachment and at a third operation the encircling 7 mm. sponge was placed around the eye. (This had just proved successful with the two aphakics of the first report). The retina stayed flat for one month, but advancing shrinkage pulled it beyond the scope of further surgery.

CASE 4

This woman had a 2-week-old lower temporal detachment in the left eye; the macula was involved and moderate nuclear sclerosis allowed only a limited view of the fundus. However, two horseshoe tears with taut opercula were found at the equator at 3 and 4 o'clock, but there was no certainty that the remaining retina was intact. The right retina showed equatorial pigmentary disturbance and some lattice degeneration in the 8 o'clock position. The left vitreous had some taut strands, but the right showed nothing grossly abnormal.

Treatment

The retina did not settle with rest in bed. At operation, cryopexy, monitored as possible, was applied to the tears and at intervals around the equator. A moderate volume of thick subretinal fluid was released at the 5.30 o'clock position and it was necessary to lower the intraocular pressure with intravenous Diamox 500 mg. and by paracentesis to facilitate the buckling procedure. A small patch of subretinal fluid remaining behind the buckle has gradually disappeared since the operation and the visual acuity in the eye has continued to improve. Sporadic subconjunctival haemorrhages have occurred adjacent to the clove-hitch ligature used to secure the ends of the implant; these have cleared spontaneously but must be related to the presence of the implant.

CASE 5

This highly myopic woman had multiple round holes of different sizes scattered around the temporal and inferior equator; there was much chorio-retinal degeneration and a posterior staphyloma. The left eye had similar, though less marked, equatorial degeneration. There was extensive bilateral vitreous syneresis.

Treatment

The retina remained elevated despite rest in bed. The surgical approach was hampered by previous strabismus surgery and the sclera was very thin. Monitored cryopexy was applied to the tears and to the suspect equator. Copious thin subretinal fluid was released at 6.30 o'clock. Minimal light coagulation was used after a week to reinforce the seal at 9 o'clock. She had one small subretinal haemorrhage adjacent to the light-coagulated area and behind the buckle at 10 o'clock in July, 1970. This has resolved without damage to the retina.

CASE 6

This 16-year-old boy had bilateral curette evacuations for congential cataract, followed by needlings, in infancy. Nystagmus and right amblyopia complicated the situation. A repeat left needling in February, 1970, was followed 3 months later by a lower half retinal detachment with an inferior large round equatorial tear, some fixed folds, and macular detachment.

Treatment

The retina did not settle with rest in bed. At operation, monitored cryopexy was applied to the tear and the retro-oral area. Subretinal fluid release at the 5.30 o'clock position was moderate and intravenous Diamox and a paracentesis were necessary to reduce the intraocular pressure. A small cyst developed around the tied ends of the sponge 2 months after surgery; this was opened and removed without interfering with the implant.

CASE 7

In this patient the right retina, which was totally detached, was torn just behind the ora from 12.30 to 4 o'clock and the free flap had fallen across the disc and macula. A finely thinned and perforated degeneration continued around the retina in the long axis of the tear, and a large round equatorial sieve-like tear completed the picture. A degeneration similar in position and type was found in the left eye. Extensive vitreous syneresis was present in both eyes.

Treatment

The retina did not flatten with rest in bed. At operation, monitored cryopexy was applied in a circle behind the ora, where it was hoped the edge of the flap would settle, and also to the equatorial tear. A large volume of thin subretinal fluid was released at 1 o'clock and the flap was coaxed over the buckle produced by the 7 mm. sponge with intravitreal air injected through the pars plana at 6 o'clock. Postoperative positioning for 9 days allowed the air to keep the flap in contact with the treated choroid and only minimal light coagulation was required to complete the seal. Prophylactic cryopexy was applied to the left eye.

CASE 8

This woman had vitreous haemorrhage and a temporal detachment which has recently arisen from an upper temporal equatorial horseshoe tear. The latter lay in the line of a strip of lattice degeneration extending down the temporal equator. Both sclerae were markedly thinned following long-standing burnt-out scleritis. The right retina was normal.

Treatment

Rest in bed produced some flattening, and monitored cryopexy was applied to the tear and the suspect equator. An attempt to place a radial sponge with an encircling No. 40 band failed, because the sutures cut out and, although the intraocular pressure had been adjusted for that procedure, it was still possible to buckle the sclera as described with the 7 mm. sponge by lowering the pressure further with intravenous Mannitol and a paracentesis. A moderate flow of subretinal fluid was obtained below the lateral rectus. One week later some leakage from the tear raised the retina as far as the macula. This settled with rest in bed and light coagulation was applied to seal the tear. A tiny fold from the buckle to the macula has prevented a better visual result.

CASE 9

This highly myopic woman had an almost total retinal detachment in her left and only eye, vision in the right eye having been lost from an untreated detachment 10 years previously. Both lenses were subluxated from birth: the right had gone on to dislocation and the left partially obscured the fundal view because of nuclear sclerosis. Clearly, only half dilatation of the pupil was permissible and with difficulty a series of fine tears were seen, placed at random behind the ora. No useful vitreous study could be made.

Treatment

The retina settled slightly with rest in bed. At operation, monitored cryopexy was applied to the tears and in a circle behind the ora. Copious quantities of subretinal fluid were released at 6.30 o'clock. Before the final tightening of the sutures holding the 7 mm. sponge, 4 per cent. pilocarpine was instilled to hold back the lens.

CASE 10

This man had a year-old detachment in his right aphakic eye. Extracapsular lens extraction, followed by six needlings, had been carried out elsewhere the previous year. The right retina was detached in the upper temporal quadrant and lower half of the eye. A large horseshoe tear with a taut operculum was found at 8 o'clock just behind the equator, and there were four further small peripheral round tears lying on a circumferential field behind the ora at 7, 9, and 12 o'clock. The vitreous was very fluid with much syneresis and the vitreous face was broken. The left eye was normal.

Treatment

Rest in bed was not helpful. At operation, monitored cryopexy was applied to the tears and to the retro-oral area. Copious thick subretinal fluid was released at 6.30 o'clock and the volume restored with intravitreal Ringer's solution injected through the pars plana. The retina was flat postoperatively and the vision improved dramatically.

CASE 11

This patient had enormous bilateral balloon detachments obscuring the discs and involving both maculae. They arose from large inferior dialyses and the retro-oral area had many erosions and much thinning. There was extensive vitreous syneresis.

Treatment

Rest in bed was not helpful. At operation on each eye, monitored cryopexy was applied around the edges and to the suspect retro-oral areas. Enormous volumes of subretinal fluid were coaxed out at 6 o'clock and the ocular volume was restored with intravitreal Ringer's solution injected through the pars plana. The left retina was flat postoperatively, but some residual subretinal fluid in the right eye took a week to absorb.

CASE 12

This young man suffered a right traumatic scleral rupture at 7 o'clock, which required suturing from the limbus almost to the equator, and there was vitreous loss. Vitreous haemorrhage thwarted fundus examination until June, 1970, when a temporal detachment involving the macula from 4 to 12 o'clock was found; tears were not clearly seen. The zonular ligament must have been damaged at the original injury, as there has been some anterior lens subluxation 2 months after the operation.

Treatment

Rest in bed was not helpful. At operation, cryopexy, monitored as possible, was applied around the extent of the scleral wound and behind the ora extending just beyond the limits of the detachment, and a moderate volume of subretinal fluid was released below the level of the lateral rectus.

Discussion

The aim of all retinal detachment surgery is to replace a functioning retina with as little trauma as possible. This implies minimal derangement of the eye at a single operation. To achieve this first-time success, therefore, the procedure should meet both the immediate and any potential cause of retinal detachment. This has been the central principle of treatment in this series of cases, and the use of the technique described has made clear its advantages in attaining the above aim in twelve out of thirteen eyes.

Intravitreal air injection without scleral buckling is becoming more popular in the treatment of retinal detachment with giant tears (Norton, Aaberg, Fung, and Curtin, 1969). In Case 7 such a method might have been employed, but it was considered that, in the presence of a large inferior equatorial tear in addition to a giant dialysis, it would have failed. The broad buckle induced by the 7 mm. sponge dealt with the tear and also allowed the edges of the giant flap to flatten more readily than similar flaps had been seen to do in other cases which we treated by air injection alone.

In Case 9, where there were multiple retro-oral tears and a subluxated lens, it is not apparent that any other technique would have been more effective. The oral pathology was easily contained by the buckle and, with the subluxated lens threatening to dislocate at all times, there was every need for speed and simplicity.

Where the sclera is thin (through myopia or scleromalacia), or where it has been accidentally or surgically injured, scleral dissection can be perilous. In those cases reported, in which the full fundus view was obscured by cataract or vitreous haemorrhage, the sponge could have been adjusted much more simply than a buried implant had a second operation been required.

There was one failure (Case 3). The encircling sponge had not been used until she came for her third operation, by which time massive vitreous retraction had set in. It is possible that the triple cryogenic insult was at least partly to blame for this development, although from our later experiences it is possible that the sponge encirclement might have been effective as a first procedure.

The two patients from the original report continue to do well and no serious complications have been observed. To date there has been no instance of glaucoma, hypotony, migration or erosion of the sponge, hampered eye movement, or ptosis in any of the twelve successfully treated eyes.

Summary

The treatment of retinal detachment with an encircling halved 7 mm. silastic sponge is described.

The technique is discussed in relation to twelve new cases (13 eyes) and the results show it to be effective, simpler than scleral dissection, and safer than the supramid suture (Manson, 1964).

I should like to thank Prof. G. I. Scott and Dr. J. F. Cullen for allowing me to manage these cases and for permission to publish the results.

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Addendum

Since the submission of this paper for publication, two further cases have been successfully treated by this method. In addition, the implant in Case 6 finally became infected and had to be removed after 6 months.

Brit. J. Ophthal. (1971) **55**, 338

Homocystinuria

Review of four cases

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Homocystinuria is an inborn error of methionine metabolism. Since it was first described by Carson and Neill (1962) in two patients in Northern Ireland, more than 100 cases have been described in the literature.

The site of biochemical abnormality was explained by Mudd, Finkelstein, Irreverre, and Laster (1964), who suggested that there was a deficiency or absence of the enzyme cystathionine synthetase which is responsible for converting the essential sulphur-containing amino acid methionine into cystine and its end-products. This results in increased concentration of methionine and homocystine in the blood and cerebrospinal fluid, and an increased excretion of homocystine in the urine. Clinically, there is a characteristic picture of mental retardation, ectopia lentis, fair complexion, fair hair, high cheek colour, thrombo-embolic episodes, and skeletal changes (Carson, Cusworth, Dent, Field, Neill, and Westall, 1963; Carey, Donovan, FitzGerald, and McAuley, 1968; Presley, Stinson, and Sidbury, 1968, 1969). General pathological findings have been described in detail in a few cases (Carson, Dent, Field, and Gaull, 1965; Carey and others, 1968; McCully 1969), and Henkind and Ashton (1965) first described the histological picture in four eyes. No satisfactory treatment is at present available for the condition, but the ocular treatment is, by choice, conservative.

During the last 2½ years, four cases have been seen in routine out-patient practice (Table).

Table *Salient features of four cases*

Feature	*Case no.*			
	1	2	3	4
Ectopia lentis	+	+	+	+
Mental retardation	+	+	+	+
Fair complexion	+	+	+	+
Fair hair	+	+	+	+
High cheek colour	+	+	+	+
Skeletal changes	None	Genu valgum High arched palate	High arched palate	Generalized osteoporosis
Spastic gait	+	–	–	+
"Marfan's syndrome"	–	–	–	–
"Marchesani's syndrome"	–	+	–	–
Parental consanguinity	–	–	–	–

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The diagnosis was confirmed biologically in the following way:

A cyanide-nitroprusside test was performed on the urine. A positive reaction indicated the presence of sulphur-containing amino acids, namely homocystine and/or cystine. These were then differentiated by paper chromatography or supervoltage electrophoresis.

Although these cases were typical enough to be suspected clinically, several unusual features were present.

Case reports

Case 1, a 25-year-old man, was admitted to the ophthalmic ward of Sutton General Hospital on March 3, 1968, with a dislocated lens and secondary glaucoma in the left eye. Symptoms of a painful red eye had persisted for 24 hours before he was brought to the casualty department of the hospital. There was no history of injury.

He was born at term after an uncomplicated pregnancy, the birth weight being 7 lb 2 oz. The milestones of early childhood were delayed. Mental retardation was first noted at the age of 3 years. He had been an in-patient in a psychiatric hospital since the age of 12 years for schizophrenia, and was having occasional violent attacks.

Examination

The left eye was injected and the lens was dislocated into the anterior chamber giving rise to secondary glaucoma. The right eye was white, but on dilatation of the pupil the lens in this eye was found to be subluxated downwards and temporally.

He was a co-operative, mild, and easy-going patient. He had features of homocystinuria (Table) namely fair complexion, fair hair, malar flush, and high-stepping spastic gait. Examination of other systems gave negative results.

Treatment

After initial hypotensive therapy with acetazolamide, the lens in the left eye was removed by *ab externo* incision and complete sector iridectomy. When the incision was completed, the lens fell back into the posterior chamber and disappeared from sight behind the iris. A gentle saline irrigation brought the lens back into the anterior chamber. It was then removed by using a vectis. There was no loss of vitreous. Recovery was uneventful.

Subsequent history

On December 31, 1968, he was re-admitted for anterior dislocation of the lens in the other (right) eye with secondary glaucoma. Management was similar to that for the left eye. The lens was extracted intracapsularly with slight vitreous loss. The postoperative period was uneventful.

Apart from occasional violent schizophrenic attacks, he is otherwise fit and well. The visual acuity is 6/9 in the right eye and 6/6 in the left with aphakic corrections. The ocular tensions and fundi are normal.

Case 2, a boy aged 4 years, was first referred to the eye out-patient department of Sutton General Hospital, because his mother thought he had a squint. He had been born at the 42nd week after a normal pregnancy, and was delivered by forceps, the birth weight being 7 lb 3 oz. He needed oxygen for resuscitation, but the neonatal period was otherwise normal. The milestones of early childhood were delayed. He was 18 months old when the parents first noted his slow development.

Examination

No squint was detected, but there was bilateral nasal subluxation of the lenses. Refraction was −5·5 D sph. in the right eye and −8·5 D sph., + 2·5 D cyl., axis 100° in the left. The fundi were normal and the ocular tension 15·9 mm.Hg (Schiötz) in each eye.

He was of short pyknotic build with strong musculature. His neck was short and his hands short and clumsy. His joints were tight. These features, along with spherophakia prompted the diagnosis of the Marchesani syndrome.

Progress

At the age of 6 years it was noted that he had some of the typical features of homocystinuria (Table). He was obviously mentally retarded with an estimated I.Q. of 46. There was no abnormality in the cardiovascular system. An abnormal electroencephalogram with paroxysmal notched irregular theta waves in all leads, with a slight similar abnormality during photic stimulation was recorded. There was also an excess of beta activity. There was an erythematous rash on his buttocks. Investigations of other systems revealed no abnormality.

Treatment and result

OCULAR

No treatment was needed apart from the prescription of glasses which were changed from time to time. When last seen, he was thought to be using the aphakic part of his pupils. An aphakic correction was prescribed as follows:

Right +12·5 D sph., + 0·75 D cyl., axis 90°,

Left: + 12·5 D sph., +1 D cyl., axis 90°.

The visual acuity was recorded as 3/60 in the right eye and 5/60 in the left.

GENERAL (carried out at Queen Mary's Hospital, Carshalton)
After the diagnosis of homocystinuria was confirmed, he was started on pyridoxine 500 mg. daily. After a week on pyridoxine, he was started on L-cystine supplements. Biochemically he became much more normal, but there was no obvious change in his mental state. He was discharged home on pyridoxine 500 mg. daily, and on this treatment he has maintained the biochemical improvement.

Case 3, the younger sister of Case 2, was referred to the eye out-patient department of Sutton General Hospital in May, 1968, at the age of 4½ years because her mother thought she was "short-sighted" as she frequently fell over. She was born after a normal pregnancy at the 42 week, the birth weight being 6 lb 13 oz. The neonatal period was normal.

Examination

There was bilateral nasal subluxation of the lenses. She was highly myopic. Refraction was −12 D sph., with visual acuity 6/24 in each eye (Sheridan Gardiner test). The ocular tensions and fundi were normal.

She showed features of homocystinuria (Table). A psychological assessment showed that, though brighter than her brother, she was mentally subnormal. Her behaviour problems were less than those of her brother, but she did have attacks of screaming.

Progress

There has been no change in her condition during the last 2 years. On her last out-patient visit, she was found to be using the aphakic part of her pupils, and an aphakic correction was prescribed. With right +8 D sph., and left + 9 D sph., the visual acuity is 6/24 in each eye, and she wears glasses happily.

Case 4, a girl aged 5 years, was noted to have a red left eye while she was an in-patient at the Queen Elizabeth Hospital for Children, Hackney, for gastroenteritis in January, 1970. There was a vague history of a blunt injury to this eye 2 weeks previously. She was born at full term and was the mother's second pregnancy at the age of 34 years. She was delivered by forceps because of maternal distress, the birth weight being 6 lb. 11 oz. The neonatal period was uneventful, but the milestones of early childhood were delayed. At the age of 1 year, she was treated for a spontaneous fracture of the femur. There was no family history nor parental consanguinity.

Examination

The left eye was obviously injected, but full examination was not possible in the out-patient department because of lack of co-operation, and an examination under anaesthesia was carried out subsequently.

The left cornea was oedematous, the anterior chamber shallow but present, and the pupil semi-dilated and fixed. The lens was subluxated downwards and temporally, and was tilted forward into the anterior chamber, firmly caught by the pupillary margin. The ocular tension was 28 mm. Hg (Schiotz). There was no clear view of the fundus.

The right eye was white, and on dilatation of the pupil the right lens was found to be subluxated downwards and temporally. The ocular tension in this eye was 14 mm. Hg (Schiotz) and the fundus was normal.

General features were typical of homocystinuria (see Table). The child had gross mental retardation, but was very excitable. Her speech was severely retarded and her vocabulary (at the age of 6 years) consisted of "mum" and "Maria". *X* ray shows generalized osteoporosis. Examination of other systems gave negative results.

Treatment and progress

Local steroid drops and acetazolamide were given and to this treatment she responded dramatically in that the left eye became white, the anterior chamber deepened, the pupil contracted, the lens fell back into its normal position, and the tension became normal. Gutt. pilocarpine 1 per cent. three times a day were then started. The eye remained white and the tension normal for one week, but the lens then again dislocated partly into the anterior chamber with secondary glaucoma. Medical treatment was not successful, and surgery was indicated. It was thought that there was an element of pupillary block, but a peripheral iridectomy failed to control the tension. Aspiration of clear lens matter was then performed under magnification. The operation was uneventful and there was no vitreous loss. The postoperative period was rather prolonged with anterior uveitis which cleared in about 6 weeks on local treatment with atropine and steroid drops.

At the present time, the patient's condition remains unchanged. The right lens remains subluxated. Contact lens fitting for the aphakic left eye is out of the question and has not been attempted.

Discussion

Spiro, Schimke, and Welch (1965) described a case of schizophrenia in a patient suffering from homocystinuria. They postulated that there might well be a relationship between these two conditions. Case 1 in the present series is so far the second recorded case of this association, and is, therefore, of some interest.

The classical signs of Marfan's syndrome have been described in a few patients suffering from homocystinuria, but none in this series showed these features. Marchesani's syndrome is even more rarely associated with homocystinuria, although Presley and others (1969) described two cases. In the present series, Case 2 has features resembling Marchesani's syndrome, with short pyknotic build, strong musculature, short neck, tight joints, and spherophakia. Indeed, he was originally diagnosed as a case of Marchesani's syndrome before the biochemical abnormality was detected.

Skeletal abnormalities which have been described include osteoporosis, pes cavus, and genu valgum. Of the four cases in this series, only one (Case 4) has definite osteoporosis, and the spontaneous fracture of femur she had suffered at the age of one year is probably explained by this bony abnormality.

Garston, Gordon, Hart, and Pollitt (1970) described a case of homocystinuria complicated by optic atrophy. This complication was not seen in any of the four cases of the present series.

All the four cases described suffer from mental retardation. Case 3 is the least affected, but she is the youngest in the series. This agrees with the findings of most authors, although the report of sixteen patients of normal intelligence in a series of 38 cases by Schimke, McKusick, Huang, and Pollack (1965) seems to be unusual.

Summary

Four cases of homocystinuria have been described, one of which also suffers from schizophrenia. A relationship between these two conditions is re-emphasized. Another case showed some of the features of Marchesani's syndrome.

I am most grateful to Mr. J. H. Dobree and Mr. R. A. Burn for their helpful criticism and guidance during the preparation of this paper. The first three cases were under the care of Mr. Burn who permitted and encouraged the reporting of them. Mrs. P. R. Marsden kindly provided the secretarial assistance.

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Brit. J. Ophthal. (1971) **55**, 343

Ocular injury in the battered baby syndrome

Report of two cases

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In the differential diagnosis of obscure skeletal and soft tissue lesions in children it is important to consider the possibility of physical abuse. The association of chronic subdural haematoma with multiple fractures in the long bones of infants was first reported by Caffey (1946), but he failed to confirm the traumatic origin he suspected. Silverman (1953) also described skeletal abnormalities in infants due to trauma, but was hesitant to blame the custodians of the child. The problem was high-lighted by the study of Adelson (1961) of 46 child murders; he emphasized the need for complete autopsies of all children "found dead" or who presented bizarre clinical pictures not explained by known syndromes. Kempe, Silverman, Steele, Droegemueller, and Silver (1962) seem to have been the first to recognize the full implications of the problem and coined the term "battered child syndrome" – now usually called the "battered baby syndrome".

At the present time in America deaths from all types of accidents account for nearly twice as many childhood deaths as cancer, and Fontana (1964) suggested that many of these accidental deaths may be due to undetected or unreported parental abuse.

Kiffney (1964) was the first to describe ocular injuries in this syndrome – retinal detachment with multiple skull fractures and bilateral subretinal haemorrhages. One eye was enucleated and provided the first opportunity for histological examination, but there were no special features apart from the detachment. Gilkes and Mann (1967) reported extreme degrees and persistence of retinal haemorrhages, with venous engorgement, snowy exudates and papilloedema, which reminded them of the fundus picture described by Purtscher (see Duke-Elder, 1954). Maroteaux, Fessard, Aron, and Lamy, (1967) and Maroteaux and Lamy (1967) described atrophic lesions in the retinal periphery in cases of the battered baby syndrome.

The purpose of this paper is to present the clinical and pathological features of two eyes which were removed from children with this syndrome.

Case 1

CLINICAL HISTORY

A male infant aged 8 months who was cared for during the day by a "baby-minder" while both parents were at work, was brought to hospital with a bulging anterior fontanelle and bilateral retinal haemorrhages. He became drowsy and was found to have bilateral subdural haematomas.

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These were drained and after a stormy course the child recovered. The haemorrhages in the right eye cleared, but in the left eye vitreous haemorrhage occurred. He was not brought for follow-up and was next seen 6 months later with a painful and swollen left eye.

Examination showed that the left eye was larger than the right (vision normal), and it was red, with corneal oedema and raised tension, aqueous flare, and a small hyphaema. The lens was pushed forward and subluxated below. Ectropion uveae and iris atrophy were present, and the vitreous was filled with blood which obscured the fundus. The eye, being blind and painful, was enucleated.

PATHOLOGY

Macroscopical examination

There was hyphaema, an eccentric pupil, and total retinal detachment with subretinal sanguineous exudate. No neoplasm was seen (Fig. 1).

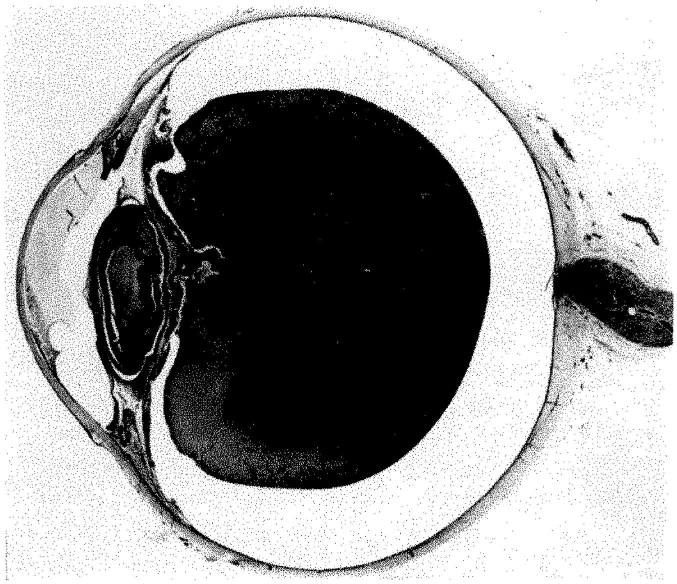

FIG. 1 *Photograph of sectioned left eye (Case 1), showing a hyphaema, retinal detachment, and sanguineous subretinal exudate. The iris shows ectropion, and the ciliary processes are drawn toward the lens by fibroblastic tissue*

Microscopical examination

The cornea showed limbal infiltration and superficial vascularization. Peripheral anterior synechiae occluded the filtration angle on both sides, and the anterior chamber contained haemorrhagic exudate. The iris showed pigment scattering, rubeosis, and ectropion, and on one side was fibrosed and contracted thus distorting the pupil. There was extreme pigmentary disturbance in the ciliary processes which were covered with fibroblastic tissue and drawn towards the lens. The latter was subluxated and cataractous and adhered posteriorly, through a vascularized hyaline membrane, to the totally detached retina which was disorganised and necrotic, showing lipid macrophages (Fig. 2) and also neovascularization into the vitreous (Fig. 3). Lipoidal macrophages and cholesterol crystals were present in the abundant subretinal fluid (Fig. 4). The optic nerve was engorged and gliosed, while the choroid and sclera were normal.

DIAGNOSIS

The picture is that of post-concussional injury. Before the history of trauma was known the histological diagnosis of Coats's disease was made.

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2. *Brit. J. Ophthal.* (1956), **40,** 159
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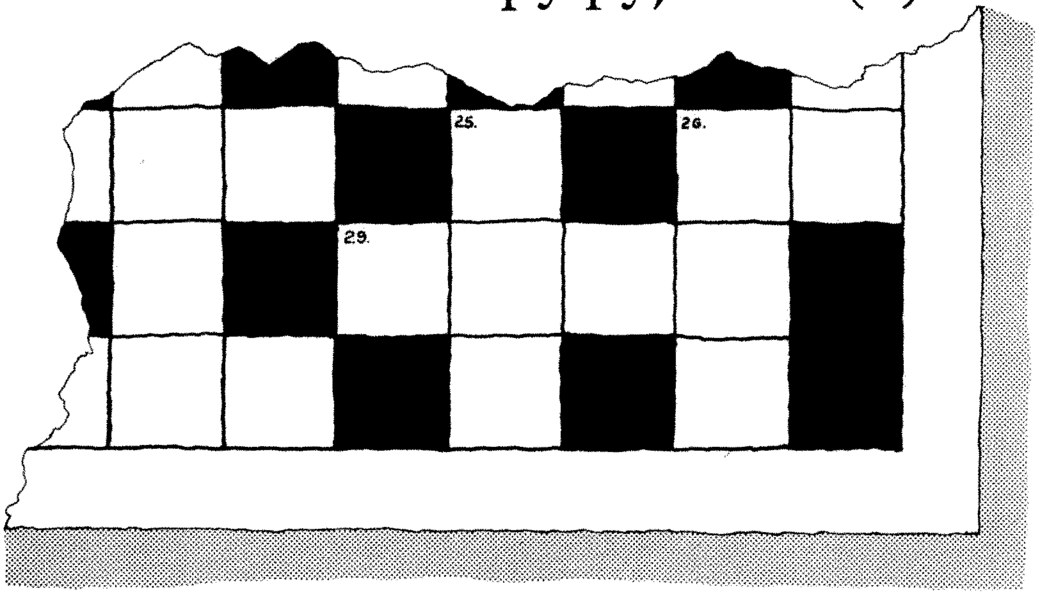

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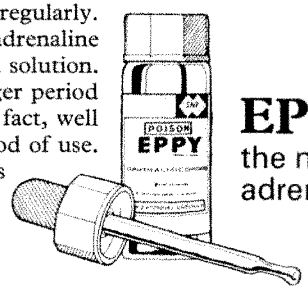

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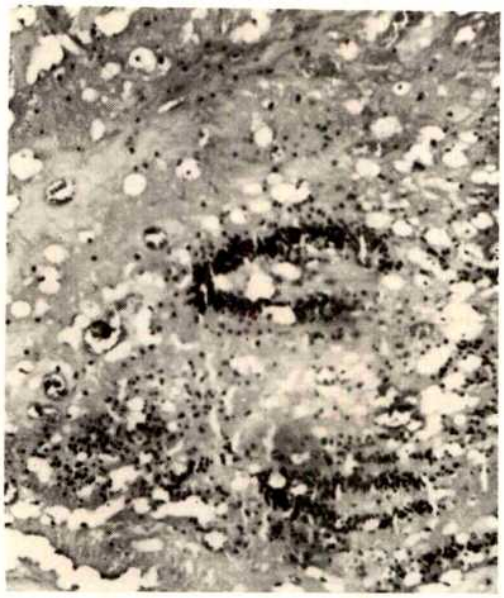

FIG. 2 *Portion of the detached retina, showing disorganization, lipid macrophages, and necrosis (Case 1). Haematoxylin and eosin.* ×90

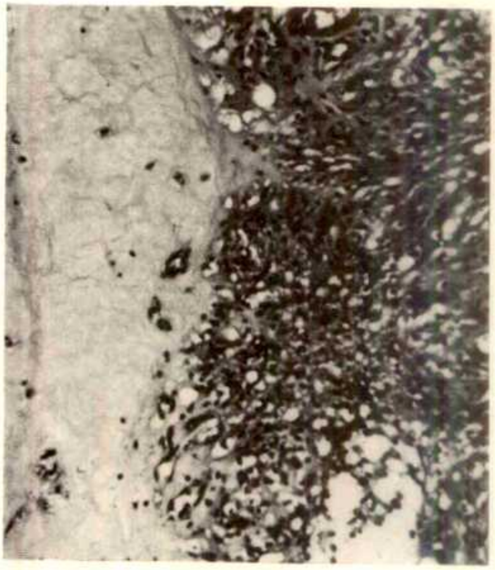

FIG. 3 *Neovascular tissue extending into the vitreous from the detached retina (Case 1). Haematoxylin and eosin.* ×90

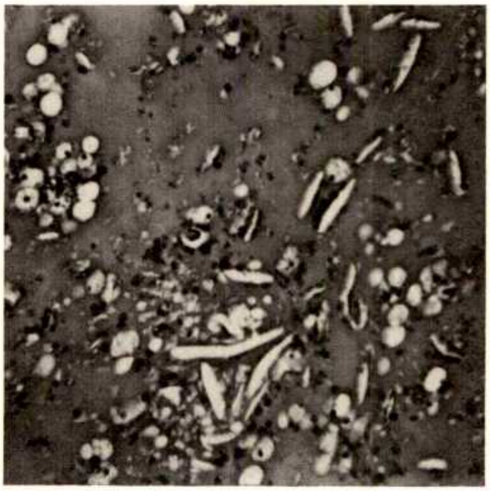

FIG. 4 *Subretinal fluid, showing cholesterol clefts and lipid macrophages ("ghost cells") (Case 1). Haematoxylin and eosin.* ×90

Case 2

CLINICAL HISTORY

A male infant 3½ months old was strangled with a blanket by his father. The baby fainted and had convulsions, and the parents spent the rest of the night shaking the child to revive him. Next day he was admitted to hospital moribund with extensive bruising and bilateral intraocular haemorrhages. His condition deteriorated and he died 24 hours after strangulation. *Post-mortem* examination showed a large subdural haemorrhage, pharyngeal bruising, and scattered haemorrhages. The left eye was examined at the Institute.

PATHOLOGY

Macroscopical examination

The eye was opened horizontally. The retina was *in situ* (Fig. 5) and showed extensive haemorrhages.

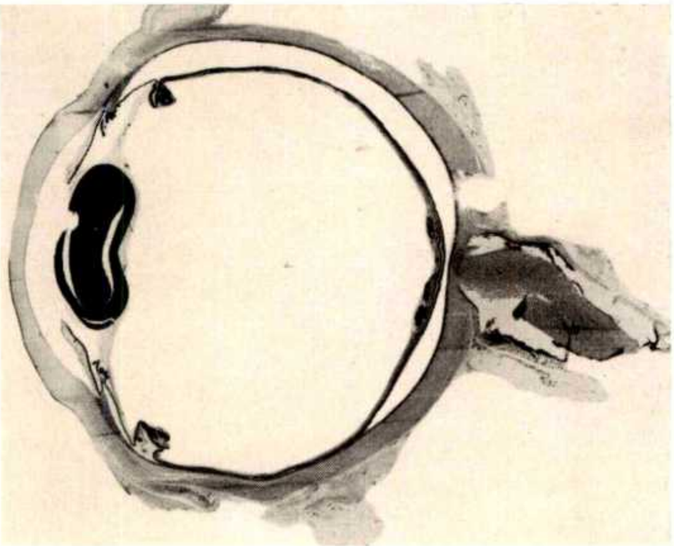

FIG. 5 *Photograph of sectioned left eye (Case 2), showing retina* in situ

Microscopical examination

The only abnormalities to be found in the globe were sited in the posterior segment, where there were extensive intraretinal, subhyaloid, and small vitreous haemorrhages (Figs 6 and 7). Some sections showed myelin extrusion at the disc.

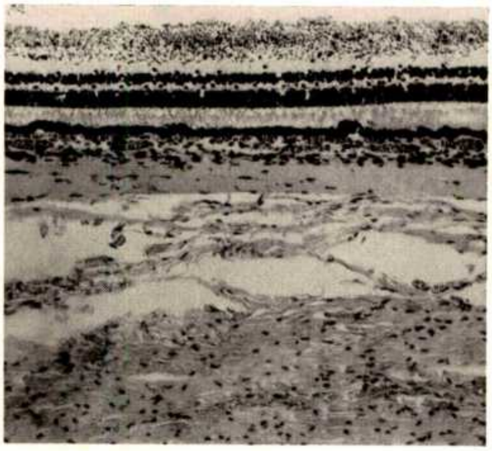

FIG. 6 *Haemorrhage in inner layers of retina (Case 2). Haematoxylin and eosin.* ×50

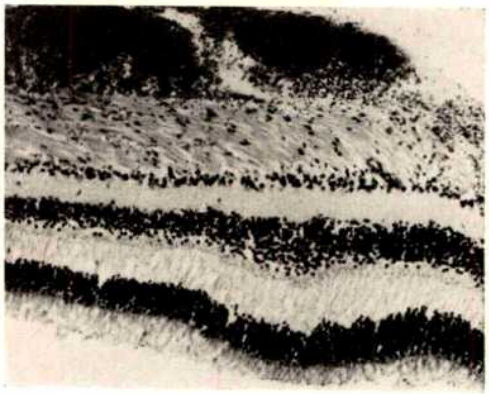

FIG. 7 *Haemorrhage in subhyaloid space (Case 2). Haematoxylin and eosin.* ×90

DIAGNOSIS

Intraocular haemorrhages due to strangulation.

Comment

These two cases illustrate the fact that the "battered baby syndrome" must be borne in mind in the differential diagnosis of ocular conditions in childhood, not only by the clinician, but perhaps more especially by the ocular pathologist, who might well be the first to recognize that the lesions are traumatic in origin. In the absence of a history of injury, as in the majority of cases, he may be trapped into making a misdiagnosis. Trauma should especially be considered in pseudoglioma, Coats's disease, lens dislocation, and all forms of old or recent intraocular haemorrhage. Case 1 was of particular interest because an erroneous histological diagnosis of Coats's disease was made in the absence of any history of trauma. The histological features of this eye simulated very closely those seen in Coats's disease, and the presence of cholesterol crystals and lipoidal macrophages in the sero-sanguineous exudate can probably be explained by chronic or recurrent haemorrhages or exudation. There seems little doubt that other cases which were previously diagnosed as Coats's disease may in fact be examples of the "battered baby syndrome".

We are grateful to Prof. Norman Ashton for his advice during the preparation of this report.

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Brit. J. Ophthal. (1971) **55**, 348

Diabetic oculo-motor nerve palsy giving rise to acute secondary glaucoma

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Diabetes mellitus is known to cause ocular complications, especially cataract, macular retinopathy, and gross intraocular vascular disease, but paralysis of the ocular motor nerve trunks is rarely due to diabetes mellitus (Whittington and Lawrence, 1963); or the underlying cause may be overlooked, as such patients are mostly over 45 years of age, appear to be in comparatively good health, and may have no other sign of diabetic disease.

The nerve most commonly affected is the sixth on one side, next the third on one side, and then either of these bilaterally; very rarely the third and sixth or the third and fourth may be affected. This paper reports the case of an apparently healthy woman who developed acute secondary glaucoma following third cerebral nerve palsy due to hitherto unsuspected diabetes, which gradually regressed when the diabetes was controlled.

Case report

A 78-year-old woman, who was otherwise healthy, was admitted to the Eye Ward of the Maelor General Hospital, Wrexham, on July 9, 1970, complaining of swelling of the right eyelids with severe pain and redness, accompanied by a feeling of nausea, for the past 24 hours.

EXAMINATION

Both lids of the right eye were swollen. There was marked ciliary injection and corneal oedema. The anterior chamber was shallow with a dilated fixed pupil. The left eye also showed a shallow anterior chamber. The ocular tension was 59·1 mm.Hg (Schiötz) in the right eye and 18·5 mm.Hg in the left. There were macular changes in the left fundus, but the right fundus could not be examined because of marked corneal oedema. Previous notes showed circinate retinopathy with visual acuity 6/60 with correction in the right eye. The visual acuity in the left eye was 6/9 with correction.

The patient's general health was excellent, except that she was hypertensive without complications; a neurological examination revealed no abnormality.

Blood pressure 240/120 (she was known to be hypertensive).

Urine + sugar (this was detected for the first time).

Radiology chest – no abnormality detected; skull – no space-occupying lesion;

There was no sign of cerebrovascular accident.

TREATMENT

With Diamox 250 mg. four times a day and 4 per cent. intensive pilocarpine therapy, the intraocular pressure was controlled and good miosis achieved.

On the third day, when the oedema of the lids subsided, it was noticed that the patient could not lift her right upper lid (Fig. 1). The upper lid was lifted (Fig. 2), and the ocular movements found to be restricted in all directions except abduction and looking down and in, indicating paralysis of the muscles supplied by the 3rd cranial nerve.

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The diabetes was first controlled by Diabenese, one tablet twice daily, and then by a sugar-free diet only. She was discharged on July 17, 1970, after the glaucoma was controlled, at which time gonioscopy revealed a moderately open anterior chamber angle. She was advised to continue with pilocarpine drops three times a day to the right eye.

PROGRESS

When she attended the out-patients clinic for the second time on September 11, 1970, she could raise her upper lid to some extent (Fig. 3) and the ocular movements had also improved by some degrees in all directions.

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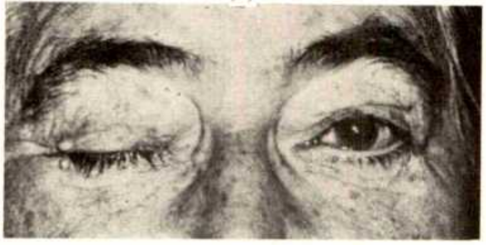

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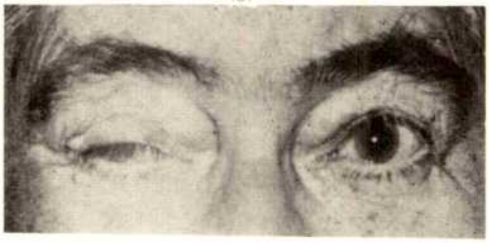

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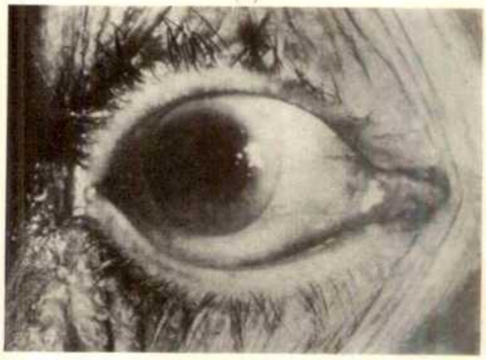

FIG. 1 *Paralysis of right upper lid*

FIG. 2 *Appearance of right eye*

FIG. 3 *Partial recovery of right ptosis*

TERMINATION

It was arranged for her to attend the clinic again on October 9, 1970, but she died on the same day in congestive cardiac failure.

Discussion

As there was no sign of cerebrovascular accident and the neurological examination did not show any abnormality, it was fairly clear that diabetes must have been the cause of the paralysis of the third cranial nerve.

The mechanism of the acute glaucoma seemed to be the blockage of the drainage of the aqueous humour through crowding of the iris in the angle of the anterior chamber as a result of paralysis of the sphincter pupillae.

Summary

A case is presented of mild diabetes which caused acute glaucoma by paralysing the 3rd cerebral nerve in an anatomically predisposed eye, with gradual recovery after treatment of the diabetes.

My thanks are due to Mr. J. F. Bras who encouraged and advised me to write this paper.

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Fibroma of the orbit

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Orbital fibromata are very rare according to Duke-Elder (1952). Among 877 orbital tumours, Reese (1963) reported only three fibromata.

Case reports

In the two following cases the general condition of the patients was good. The total and differential blood counts were normal; the blood Wassermann reaction and the tuberculin test were negative. There was no history of trauma, and the proptosis was painless and slow to develop.

Case 1, *a 25-year-old male* (Fig. 1), had a left proptosis which had developed slowly during the past 3 years. The right eye was normal, and the visual acuity 6/6.

The left eye showed conjunctival chemosis, inward proptosis of 26 mm. (Hertel), and limitation of ocular movements downwards and outwards. The visual acuity was 6/12. The fundus showed engorgement of the retinal vessels. A hard mass was felt between the eye and the outer lower orbital margin.

Skull *x* rays showed no abnormality of the orbital bones.

The mass, which was removed through an anterior orbitotomy, measured 3 × 2 × 1 cm. It was encapsulated, hard, and adherent to the periorbita of the lower outer orbital wall.

HISTOPATHOLOGICAL EXAMINATION

There were fibrocytes in a fibrous stroma (Fig. 2).

RESULT

There was no recurrence after 5 years' follow-up (Fig. 3).

Case 2, *a 6-year-old boy* (Fig. 4), had a slowly developing left proptosis of 4 years' duration. The right eye was normal, with visual acuity 6/9.

The left eye showed downward proptosis of 24 mm. (Hertel) and limitation of ocular movement upwards. The visual acuity was 6/9 and the fundus normal. A hard mass was felt between the eye and the upper orbital margin.

Skull *x* rays (postero-anterior view) showed a dilated left orbit.

The tumour when removed was found to be hard and encapsulated. It measured 2 × 2 × 1 cm., and was adherent to the periosteum of the upper orbital wall.

HISTOPATHOLOGICAL EXAMINATION. The tumour was an orbital fibroma (Fig. 5).

RESULT

There was no recurrence after 5 years' follow-up.

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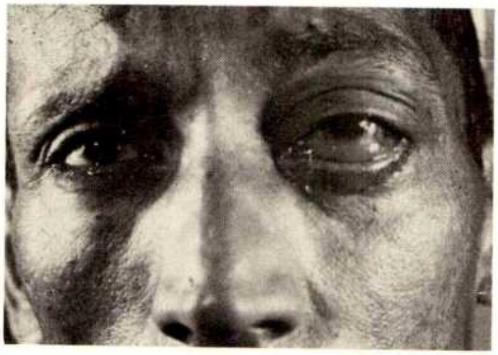

FIG. 1 *Case* 1. *Left proptosis of 3 years' duration in a male aged 25 years. This was due to a flat orbital fibroma adherent to the periosteum of the inferolateral orbital wall*

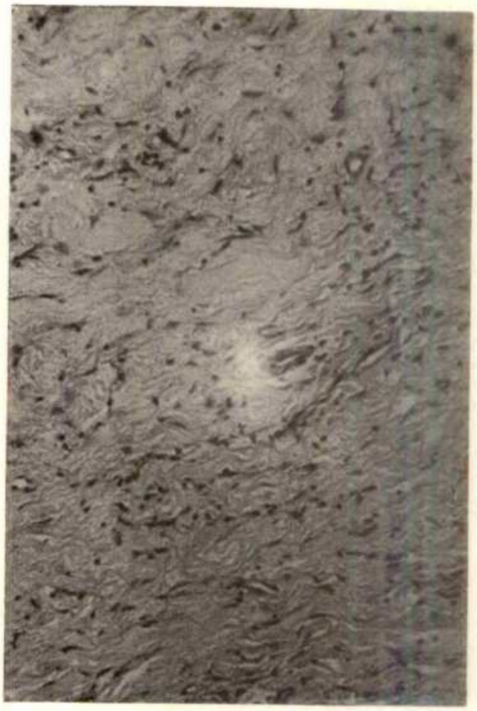

FIG. 2 *Case* 1. *Orbital fibroma.* × 120

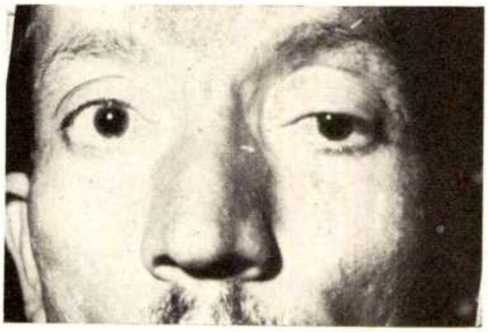

FIG. 3 *Case* 1. *Patient's appearance 5 years after removal of orbital fibroma*

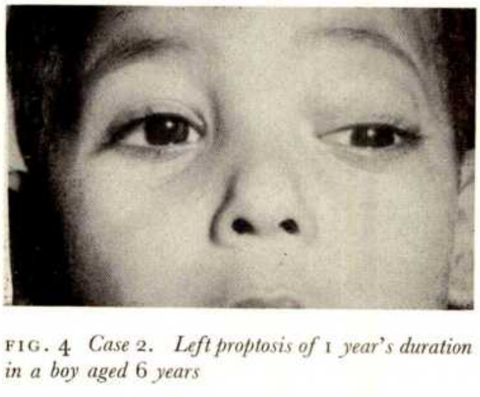

FIG. 4 *Case* 2. *Left proptosis of* 1 *year's duration in a boy aged* 6 *years*

(5)

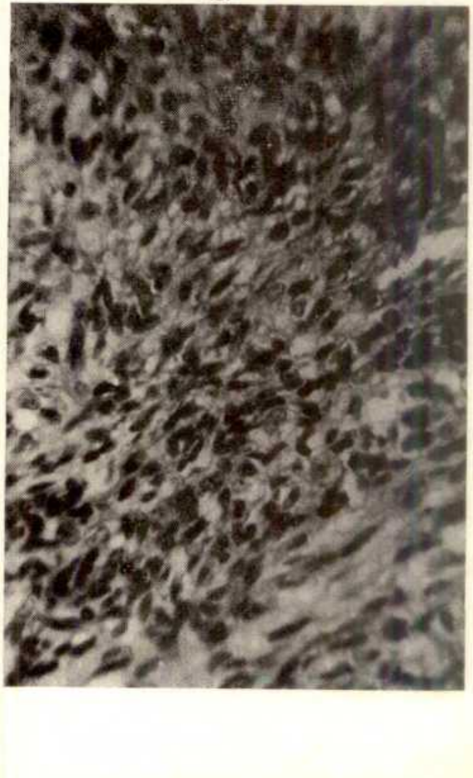

FIG. 5 *Case* 2. *Orbital fibroma.* × 120

Discussion

Fibromata of the orbit usually arise from the upper part of the periorbita (Stokes and Bowers, 1934; Garcia Miranda, 1947). They may also arise in the muscle cone (Fowler and Terplan, 1942) attached to the sheath of one of the rectus muscles (Reese, 1941) or of the optic nerve (Forrest, 1949). They usually appear before the age of 16 years and rarely after the age of 30 years.

My series of 900 histopathologically diagnosed orbital tumours has included only these two cases of orbital fibroma. Histopathologically this condition has to be differentiated from fibrosing haemangioma, fibrosing haemangio-endothelioma, and fibrosis in a pseudo-tumour.

Summary

(1) Two very rare cases of orbital fibromata are described.

(2) In both cases the tumour occurred in relation to the periosteum of the orbital bones.

(3) The patients' ages were 6 and 25 years.

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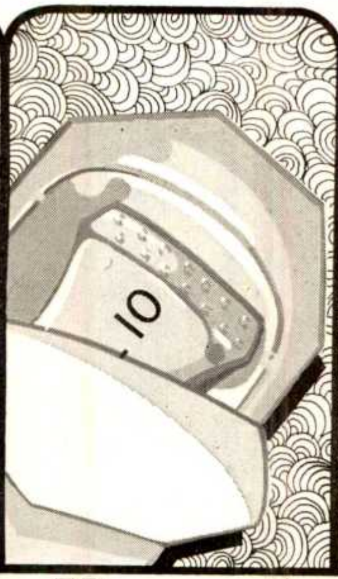

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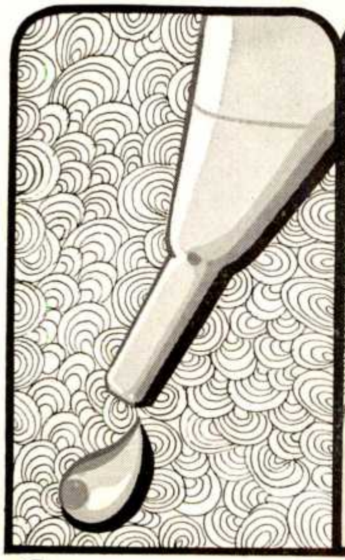

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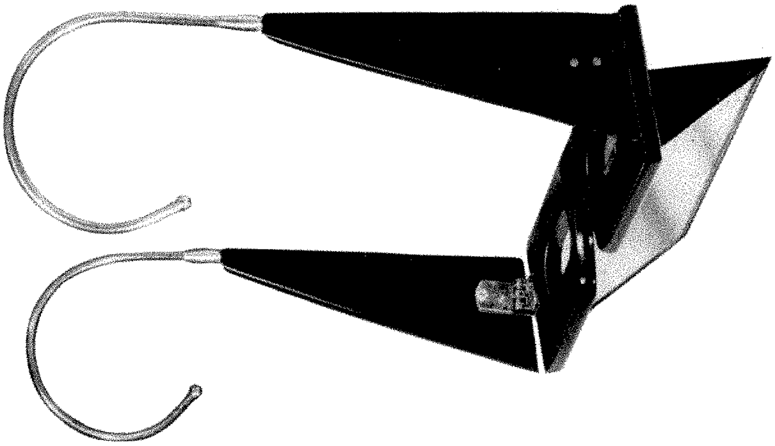

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Leiomyoma of the iris

Report of a case

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From Mexico City and †‡Santiago, Chile*

Leiomyomata of the iris are infrequent (Erdbrink and Harbert, 1955), and represent, according to the literature, between 2·3 and 14 per cent. of all iris tumours. They have been reported only in white subjects aged between 10 and 77 years, females being more frequently affected. They involve most commonly the lower half of the iris, more often on the temporal side, and may arise from either the sphincter or the dilator muscle. Despite the neuroectodermal origin of the iris muscles, the tumour is a typical leiomyoma, showing histological features similar to those originating in the mesodermal smooth muscles. They appear as a well circumscribed, slightly elevated, greyish-white or pink, vascularized mass, hyphaema being not unusual. The pupillary reflexes are not usually affected and ectropion uveae is frequent. Clinical symptoms are absent (Ferrer, 1949) and vision is not impaired unless hyphaema, cataract, or secondary glaucoma develops.

The clinical diagnosis is difficult because in a high percentage of cases it is impossible to differentiate an iris leiomyoma from a lightly-pigmented malignant melanoma (Duke-Elder, 1966).

The treatment of choice is total excision of the tumour when it is well limited, but if the growth is active, with diffuse invasion of the iris and/or extension to the anterior chamber angle, the eye should be enucleated.

Prognosis is good if the tumour is removed before invasion of the neighbouring structures has occurred. No metastases have been reported but there may be local recurrence when the tumour is not totally excised.

Histologically (Brown, Kellenberger, Hudson, and Matthews, 1957; Nordmann and Brini, 1962; Ashton and Wybar, 1966; Cullmann, 1968), iris leiomyomata show elongated interlacing spindle cells, with oval, sometimes palisaded nuclei, and eosinophilic cytoplasm containing numerous myoglial fibrils best demonstrated with Mallory phosphotungstic-acid haematoxylin, Masson's trichrome stain, and gold impregnation.

Case report

A 68-year-old white male showed a discoloured slightly raised tumour mass in the iris of the right eye of several months' duration, with moderate pupillary deformity and slight ectropion uveae; 6 weeks later the iris mass was found to be larger and there was more marked ectropion and pupillary traction. Slit-lamp examination revealed pigment dust on the posterior surface of the cornea. The anterior chamber showed normal depth, the angle was open, and there was an aqueous flare.

Presented by C.C.V. at the 7th Meeting of the Southern Ophthalmic Pathology Society, in Lima, Peru, January 8–11, 1969.

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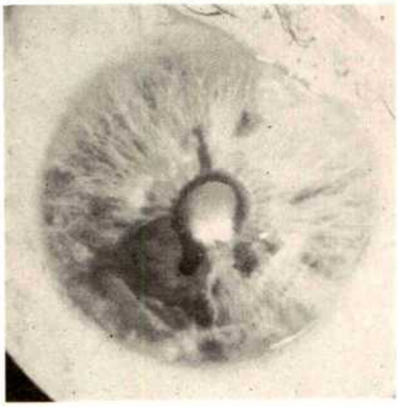
There was a pinkish-yellow, poorly circumscribed elevated mass on the lower temporal quadrant of the iris, between the pupillary margin and the collarette projecting into the anterior chamber (Fig. 1). Schiötz tension was normal in both eyes. The corrected visual acuity was 5/7·50 in the right eye and 5/5 in the left.

The diagnoses of leiomyosarcoma or melanoma of the iris were considered and a wide excision of the tumour was performed on February 5, 1968, under general anaesthesia (Figs 2 and 3).

(1)



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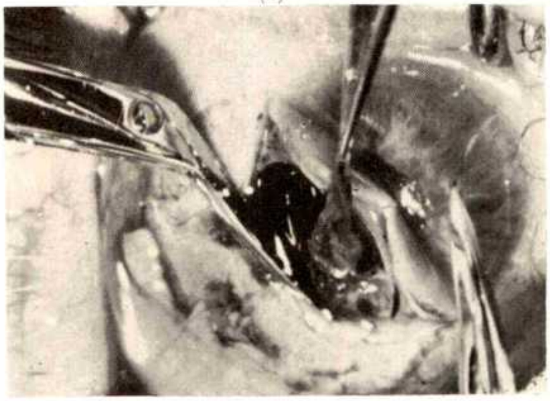

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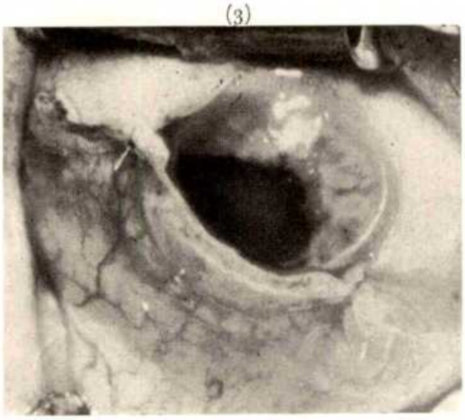


FIG. 1 *Slightly elevated tumour mass in lower temporal quadrant of right iris*

FIG. 2 *Surgical excision of neoplasm*

FIG. 3 *Postoperative photograph, showing wide iridectomy and total removal of neoplasm*

PATHOLOGICAL FINDINGS

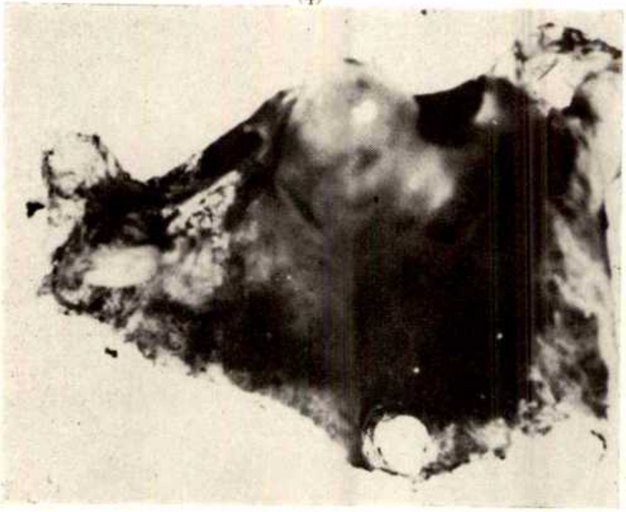
Macroscopically the formalin-fixed specimen consists of a triangular-shaped flat fragment of dark-greyish tissue, measuring 7 × 4·5 × 2 mm., with a central lobulated whitish firm excrescence, measuring 4 + 3 + 2 mm. (Fig. 4, opposite).

Microscopically, arising from the dilator muscle and spreading through the iris stroma to reach the anterior surface of the iris (Fig. 5), there is a neoplasm composed of interlacing bundles of spindle cells with elongated basophilic nuclei with blunted ends and fibrillar acidophilic cytoplasm. No mitoses are seen. A wide area of tumour-free iris tissue is present on both sides of the neoplasm. Special stains (Masson's and Gomori's trichrome) revealed longitudinal fibrils within the cytoplasm of the tumour cells (Fig. 6, overleaf). On cross-section the cytoplasm is seen to be granular (Fig. 7, overleaf).

Diagnosis

Leiomyoma of the iris, arising in the dilator muscle.

(4)



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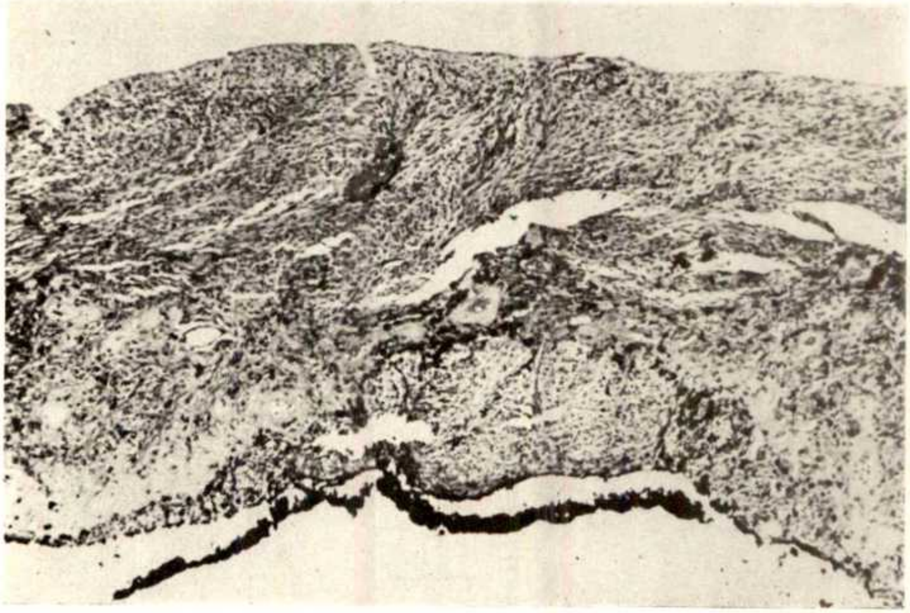

FIG. 4 *Surgical specimen, showing tumour mass protruding centrally*

FIG. 5 *Tumour cells arising from dilator muscle and spreading through stroma to reach anterior surface of iris. Haematoxylin and eosin.* ×80

Comment

This iris leiomyoma is typical both clinically and pathologically. Its location in the lower temporal quadrant is the most common as recorded in the literature.

The eye was treated surgically by performing a wide iridectomy to obtain a total excision of the tumour. This is the same treatment as is recommended in other well localized iris tumours, including malignant melanomata, for which reason the clinical difficulty of establishing a precise differential diagnosis is of limited importance. Only a careful histological study, using special stains to demonstrate the intracytoplasmic longitudinal fibrils, will permit the correct diagnosis. When the tumour is removed *in toto* the

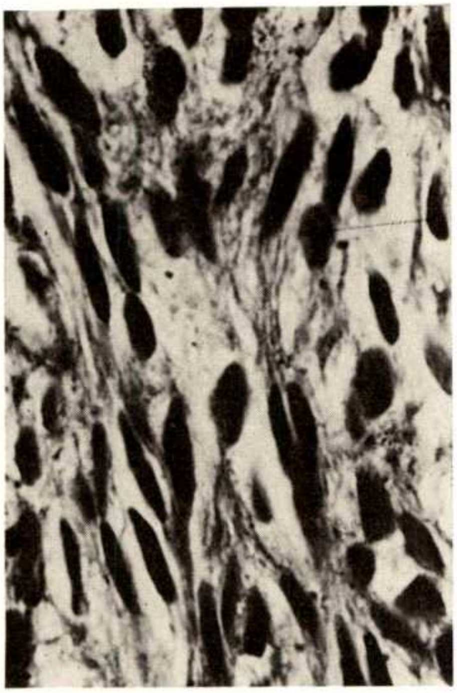

FIG. 6 *Elongated tumour cells with longitudinal fibrils within cytoplasm. Note that most of the nuclei show blunted ends. Masson's trichrome.* ×920 *(oil immersion)*

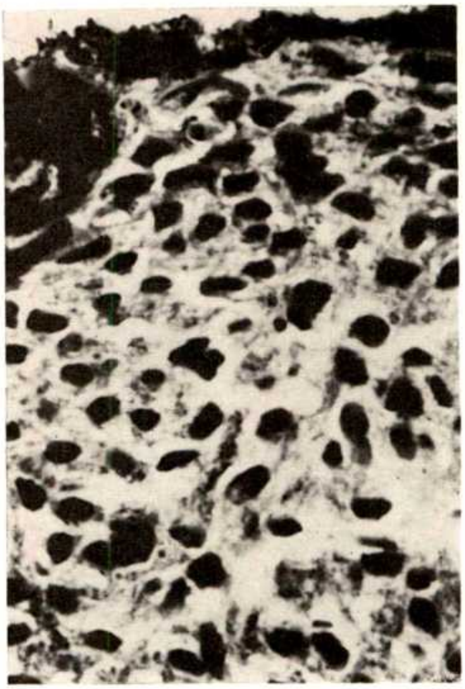

FIG. 7 *Cross-section of tumour cells, showing granular cytoplasm. Masson's trichrome.* ×920 *(oil immersion)*

prognosis is good. In the present case, on August 5, 1970, that is 2½ years after the iridectomy, no signs of recurrence were present, the anterior chamber was deep and there was no aqueous flare or posterior synechiae.

Summary

A case is presented of leiomyoma of the iris confined to the lower temporal quadrant in a 68-year-old man, and the clinical and histological characteristics of this rare neoplasm are described.

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Book reviews

Correction of Subnormal Vision. By N. BIER. 2nd ed., 1970. Pp. 287, figs, bibl. Butterworths, London. (£5.00)

The second edition of Norman Bier's "Correction of Subnormal Vision" will be welcomed by all those concerned in visual aid work. The book is a well-illustrated description of the different types of optical device available for the correction of subnormal vision. Ophthalmologists often tend to fight shy of this branch of the specialty, and they may find the technicalities a little difficult to comprehend as knowledge of the optical principles of many of the devices is often assumed in the text. Although the bibliography has been extensively revised and most of the modern visual aids are described, some of the discussion on the management of subnormal vision, particularly in children, is dated, and very little reference is made to the newer surgical techniques which are beginning to play an important part in the treatment of subnormal vision.

On Helping the Dyslexic Child. By T. R. MILES. 1970. Pp. 70. Methuen Educational Ltd., London. (£1.05)

This little book is designed to help the teacher of the dyslexic child and is not concerned with the neuro-ophthalmic aspects of the condition. Indeed, the author notes that poor vision is only occasionally a cause of poor reading.

The thesis of this book is that dyslexia is a form of word blindness, so that the look-and-say method of teaching to read is of little help. The alternative method is proposed of phonetic cues whereby individual letters are built up as sounds to complete words. The child must learn to say each simple sound carefully, paying attention to the movement of his lips, tongue, and throat. He is encouraged to write his own "dictionary" where words of similar sound are written together.

This is a practical approach to a very difficult problem. Professor Miles stresses that any attempt at treatment is better than none and this book may well help the inexperienced teacher, who may also be the parent.

Perception and its Disorders. Res. Publ. Ass. nerv. ment. Dis., Vol. 48. Edited by D. A. HAMBURG, K. H. PRIBRAM and A. J. STUNKARD. 1970. Pp. 405, 134 figs, refs. Williams and Wilkins, Baltimore; Livingstone, Edinburgh. (£10.00)

This book derives from the 1968 meeting of the Association for Research in Nervous and Mental Diseases when the topic selected was perception. All sensory modalities, including hunger and dreams, were considered, but the emphasis was mainly on vision. The visual papers range from the psychological aspects of perception, through animal experiments, to investigations of human disease. Much of the work described may well be unfamiliar to the ophthalmologist, as references to ophthalmic literature are sparse. Unlike many psychologically orientated publications, this work is not concerned with using sensory processes as tools but with the mechanism of these processes; the approach is defined in the second and third chapters on colour vision, one being a review of the basic mechanisms of colour vision and the other a convincing theory to account for the phenomenon of Benham's top.

It is unlikely that the clinician will feel constrained to add this book to his library, but it will amply repay reading. Furthermore, all the contributors have maintained a high level of readability so that even the inevitable abbreviations seem far less obtrusive. This is the 47th research publication of the Association and it fully maintains the very high standards established in previous years.

Arteriography of the External Carotid. Anatomical, Radiological, and Clinical Study. (Artériographie de la carotide externe. Étude anatomo-radiologique et clinique.) By C. AARON, D. DOYON, H. FISCHGOLD, J. METZGER, and J. RICHARD. 1970. Pp. 118, 135 figs, refs. Masson, Paris. (Frs. 66)

This is an excellently illustrated account of the anatomy of the external carotid distribution, methods of angiography, and findings in the normal and abnormal. There is also a correlative note on thermography and a less relevant short chapter on comparative anatomy. Although most of the book is of no practical importance to the ophthalmologist, it is of great interest to be made aware of the advances in another specialty. Although the orbit is supplied mainly by the internal carotid there are anastomotic branches from the external carotid, and examples of the importance of these are shown.

A useful feature is a book mark with a list of abbreviations used in the illustrations.

Congenital and Paediatric Glaucomas. By R. N. SHAFFER and D. I. WEISS. 1970. Pp. 221, 253 figs, 3 col. pl., refs. Mosby, St Louis (Kimpton, London). (£9.25)

This is a classical treatise on a difficult subject, beautifully presented and packed with most valuable information. The work is notable for its scrupulous honesty and accuracy of data and for its wide coverage of many associated conditions and the rarer syndromes.

The illustrations are of a strikingly high standard and help to bring home forcibly many of the important points made in the text.

Although the work is not essentially controversial in nature, the authors introduce at one point the tantalizing enigma of the precise cause of cupping of the disc in ocular hypertension. The reader may be justified in wondering whether fluorescein evidence of delay in disc circulation is also evidence of reduced circulation.

He may also wonder whether the point has been made in favour of the contusion angle deformity in traumatic glaucoma (a syndrome which the reviewer regards with deep suspicion). But these matters add piquancy to a delightful work.

There are several points which the reviewer found of great interest; for example the fact that a cup/disc ratio of more than 0·3 is so rare in normal infants, and the important part played by rubella in many infantile glaucomas, together with the intriguing suggestion that rubella glaucoma and cataract are mutually exclusive.

This book certainly makes absorbing reading and is highly recommended for ophthalmologists at all levels.

Symposium on Ocular Anti-inflammatory Therapy. Edited by H. E. KAUFMAN. 1970. Pp. 272 + xiv, 75 figs (some col.). Thomas, Springfield, Ill. ($19.00)

The immense benefits which the development of anti-inflammatory agents have brought to the treatment of ocular inflammation have been offset to some extent by their complications, both systemic and ocular. The main purpose of this symposium was to evaluate the potency of different preparations and different methods of use in order to combine the optimum therapeutic effect with the minimum toxicity.

The adverse systemic effects can be reduced by local administration, and injections of a depot preparation into Tenon's capsule seem to have advantages over subconjunctival injections in the treatment of uveitis. Two papers suggest that steroids and antimicrobial therapy can be combined safely in the treatment of infective conditions, provided that the patients have normal immunoglobulins.

Although some promising results have been obtained with immunosuppressive agents in corneal grafting and ocular inflammation, the presently available drugs are too toxic and too limited in their effectiveness for most clinical requirements. Antilymphocytic serum has not so far been shown to be of value in corneal grafting or ocular inflammation.

The many detailed experimental and clinical studies presented in this symposium will be useful for those specializing in the field of ocular inflammation, but the clinical ophthalmologist will not find any easy solution to the treatment of inflammatory disease.

Ocular Pharmacology. By W. H. HAVENER. 2nd ed., 1970. Pp. 556, 304 figs, refs. Mosby, St Louis (Kimpton, London). (£13.25)

The first edition of this book brought together a very wide range of information concerning the drugs used in ophthalmology. The mode of action, route of administration, dosage, and toxicity were very clearly presented, with emphasis on the practical application in routine treatment.

The second edition has been brought up to date and supplemented by a section on the treatment of common ophthalmological conditions. Again the accent is on practical management, and the balanced and well-documented views of the author should be read by all ophthalmologists. The introductory chapter on the evaluation of therapeutic response is a salutary condemnation of "clinical impressions" unsupported by properly controlled trials.

This is an excellent and well-written book, enlivened by many examples from the author's own experience, and it provides a reference manual to modern work on ocular pharmacology and a practical guide to ocular therapeutics. It is well produced and well indexed, and has an extensive list of references at the end of each chapter.

Ophthalmic Plastic Surgery. By S. A. FOX. 4th ed., 1970. Pp. 590, 308 figs, refs. Grune and Stratton, New York and London. ($29.75)

This new edition is a considerable improvement on its popular predecessors. After introductory chapters on anatomy, technical details, grafting, and basic techniques, there follow chapters dealing with all minor and major lid, lacrimal, socket, and orbital problems classified on a sensible anatomical basis. The book is very readable and practical in its outlook. The line diagrams are uniformly successful but the standard of photographs is rather variable for a book of this expense (a point that the author admits). It is a pity that modern radiotherapy in the treatment of lid tumours is not given more prominence (only six pages) as—in Great Britain at least—this would seem to be the ideal form of primary treatment. However, these are small criticisms of an excellent book.

Management of the Patient with Subnormal Vision. By G. FONDA. 2nd ed., 1970. Pp. 167, 114 figs, bibl. Mosby, St. Louis (Kimpton, London). (£5.85)

"The nation's blind population is increasing at nearly twice the rate of the general population"—an emotive statement and one that sets the theme for this excellent book on the management of the patient with subnormal vision.

This is a difficult subject for the clinical ophthalmologist largely because of the supposed requirement for the knowledge of advanced optics, and also for the length of time that needs to be devoted to each patient. Gerald Fonda's book sets down in a precise, uncomplicated form the background to the prescribing of visual aids. In the course of bringing our knowledge up to date many myths are exploded. We learn of the advantages of high plus lenses to aid reading even though the print must be brought very close to the eye, and the patient must "read with his nose". We learn of the difficulties of telescopic aids which may effectively make an individual legally blind, and there are provocative thoughts on the use of large print and the question of learning Braille.

The volume is well-produced, excellently illustrated, and written in a logical and lucid style. Each chapter is succinct and the final questions-and-answers section is particularly recommended.

All in all a very good book.

Orbital Fractures. By H. H. Hötte. 1970. Pp. 394, 75 figs, bibl. Royal Vangorcum, Assen, The Netherlands. (Florins 74)

This valuable treatise begins with some discussion regarding the primary functions of the human face, including vision, respiration, smell, intake of food, and speech. The face also has aesthetic functions. The osteology of the face is described with special emphasis on the orbital walls. The anatomy of the orbital adnexa and the orbital contents is discussed. Fracture mechanisms and types of fracture are listed and their aetiology is presented. The importance of the careful clinical examination of patients is emphasized and the clinical record sheet used in Amsterdam is shown. The value of the opinions of otolaryngologists, neurologists, and plastic surgeons is stated. The various complications of facial injury are described, and the useful work of the orthoptic department is emphasized. Radiological examination of facial injuries is essential and this is described and illustrated. Many patients with facial injury suffer damage to the optic nerves with or without fractures of the optic canal. The treatment of all facial injuries is discussed and the surgical methods used are shown in detail. The book is concluded by statistical evaluation of 309 cases of orbital fracture, which shows most interesting results. The author also inserts a chapter on the responsibility of the ophthalmic surgeon in cases of orbital fracture.

Notes

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Obituary

Edwin Harry Leonard Cook, 1916–1971

E. H. L. Cook was one of the better known and best liked ophthalmologists in the north of England. He graduated at the University of Liverpool in 1940 and thereafter joined the Volunteer Reserve of the Royal Air Force. His final period of service was in India where he became attracted to ophthalmology, and on returning home he pursued that subject, becoming senior registrar in the (then) Eye, Ear and Throat Infirmary in Liverpool in 1947. After holding several surgical posts in the surrounding region, he became a consulting ophthalmic surgeon to St. Paul's Eye Hospital in Liverpool in 1958, and when his untimely death occurred he was senior consultant ophthalmic surgeon to the Liverpool Regional Hospital Board and the United Liverpool Hospitals and also lecturer in ophthalmology to his old university.

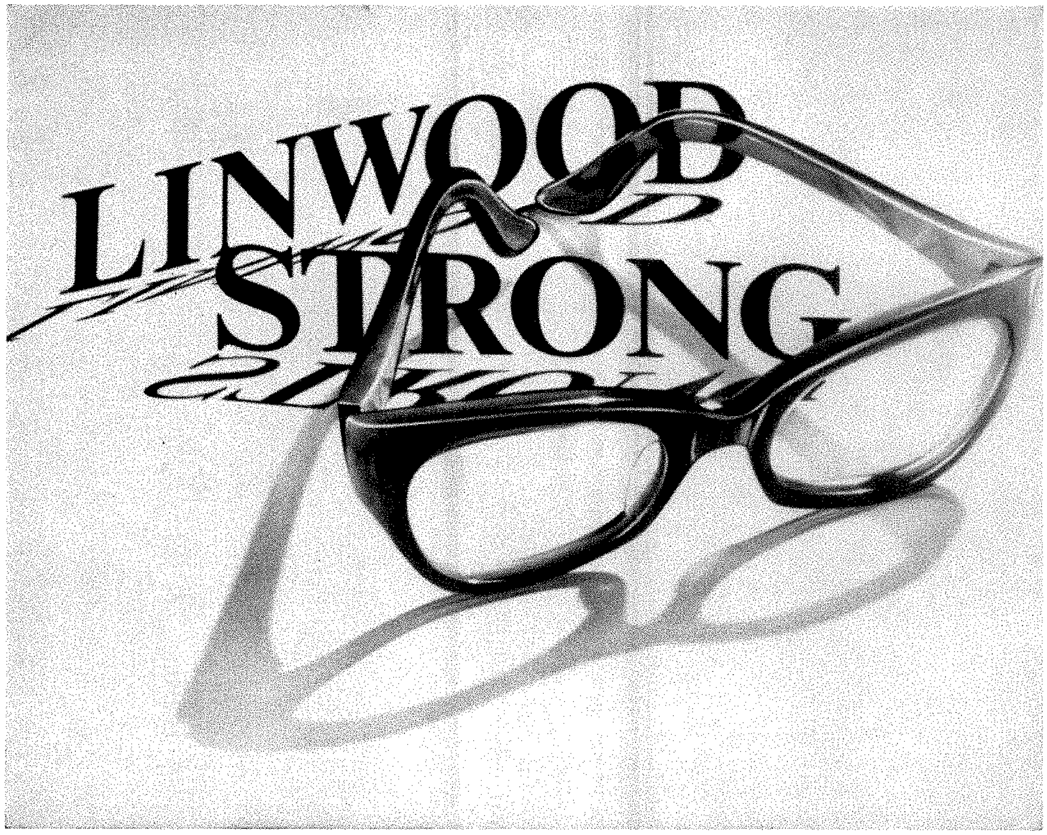
Correction

In the article by A. N. Barber, C. Catsulis, and R. J. Cangelosi, which appeared in the February issue (*Brit. J. Ophthal.* (1971) **55**, 91), please amend the following:

p. 93, 1. 7, *for* sytoplasm *read* cytoplasm

p. 98, 1. 3, *for* would *read* could

It is regretted that the authors' corrected proofs were delayed by the Post Office strike.



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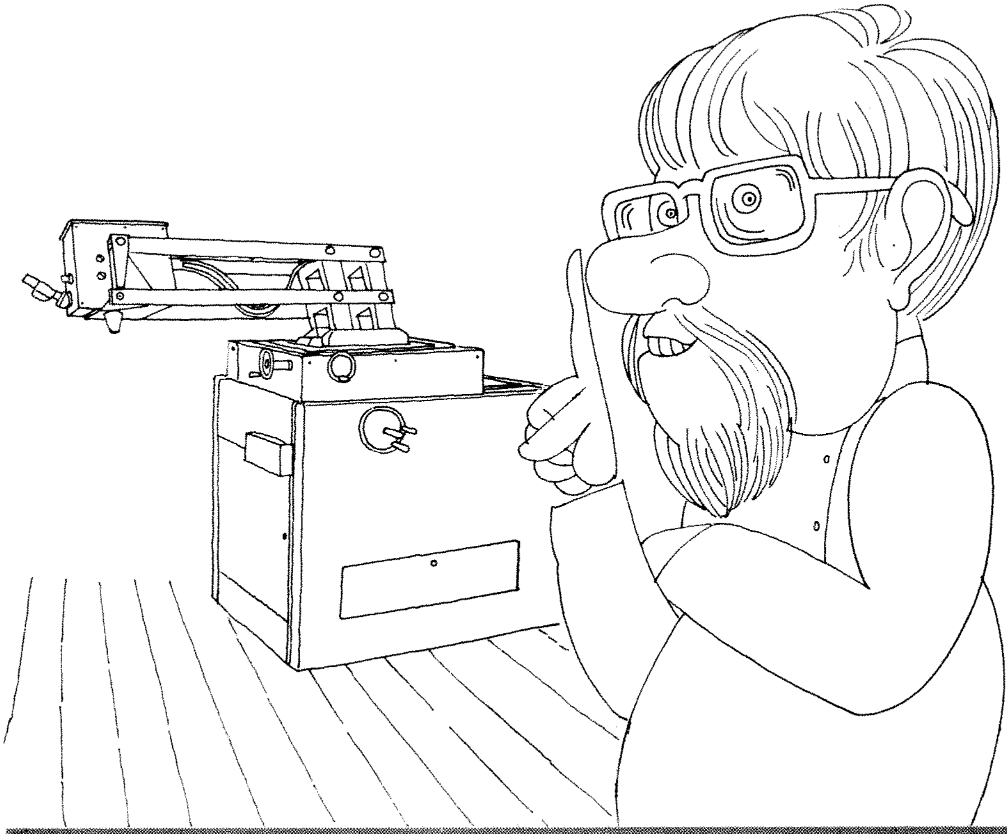

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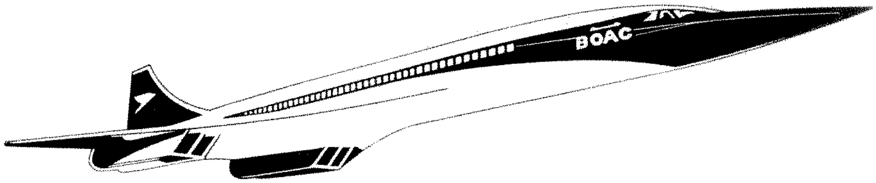

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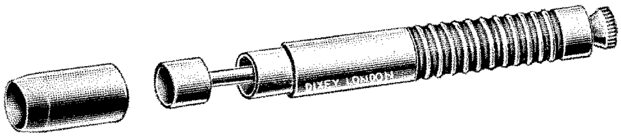

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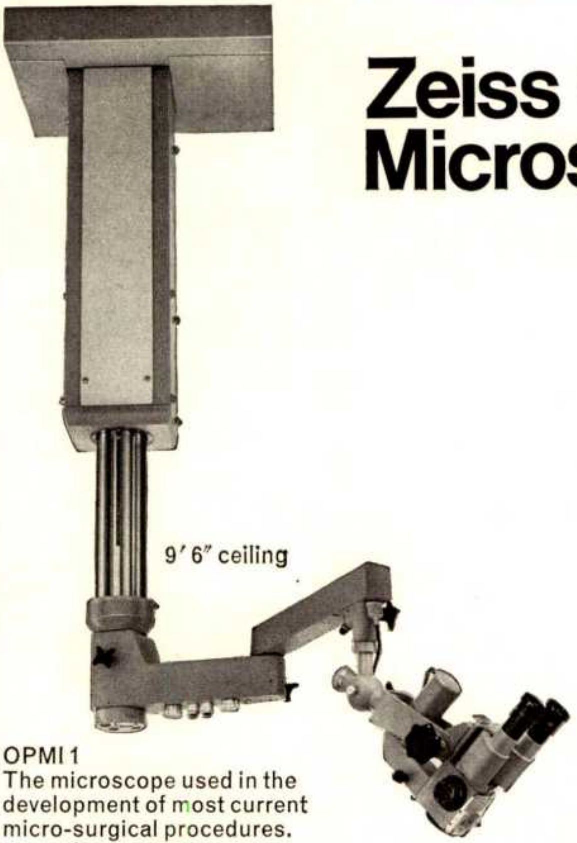

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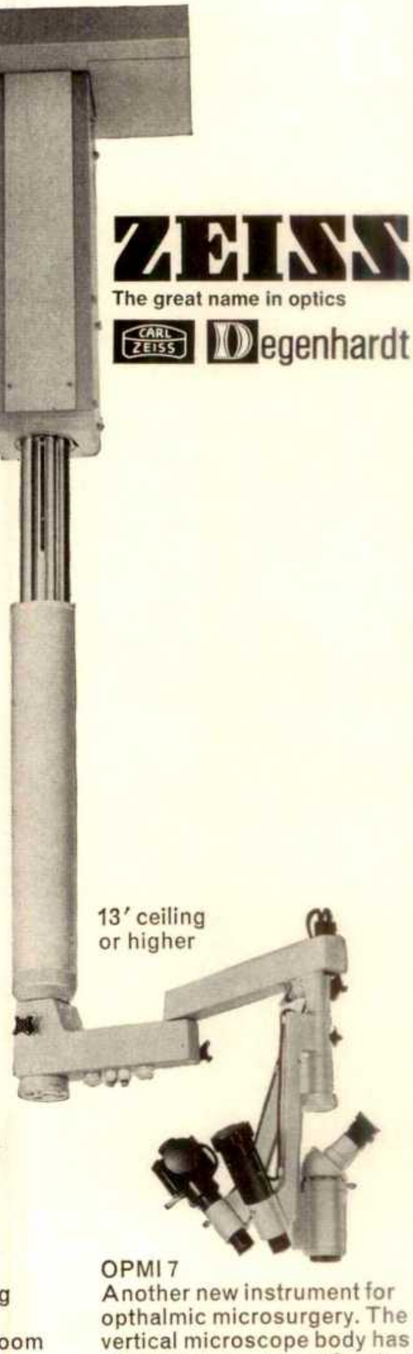

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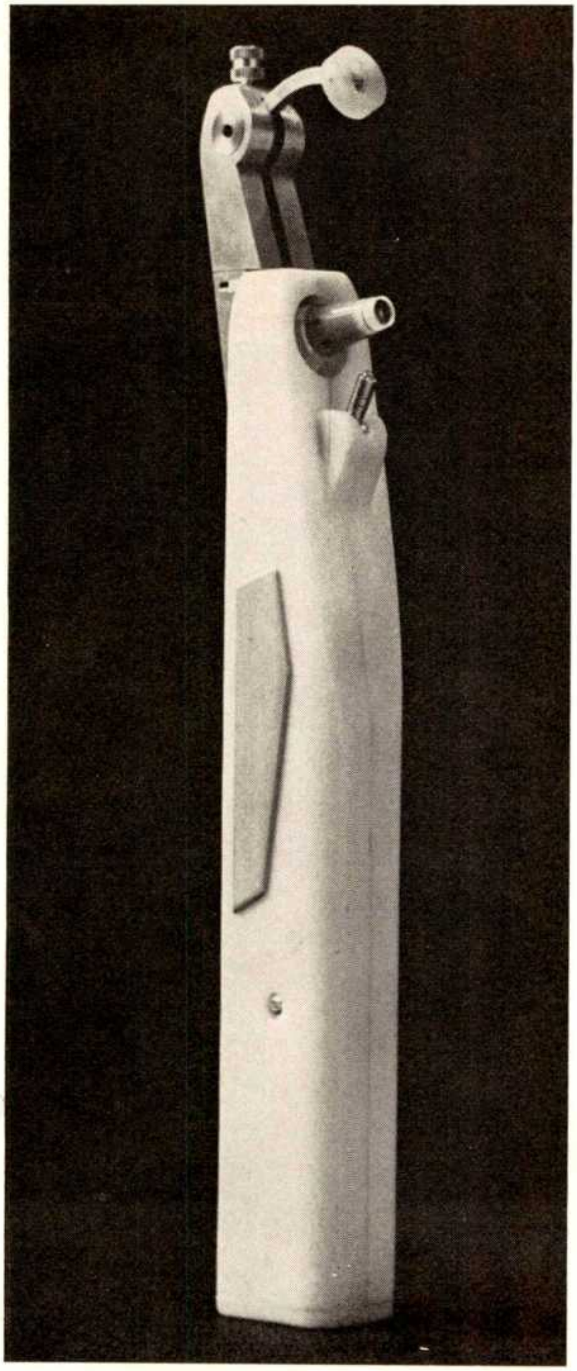

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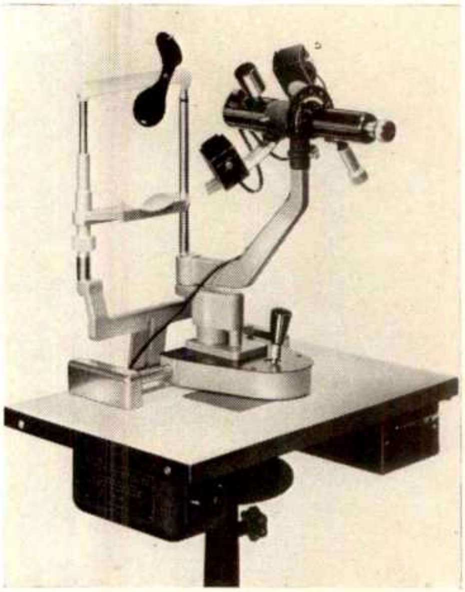

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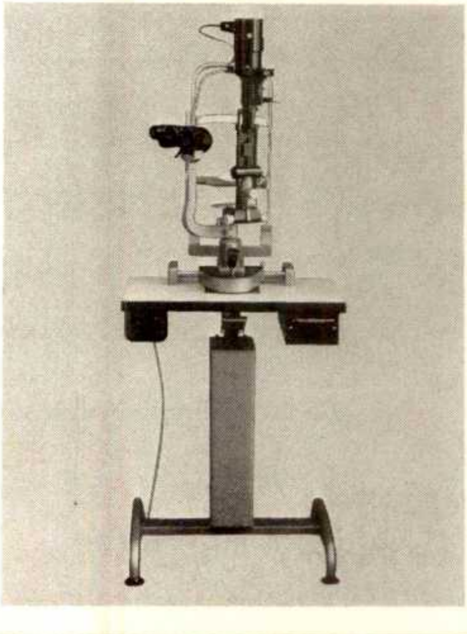

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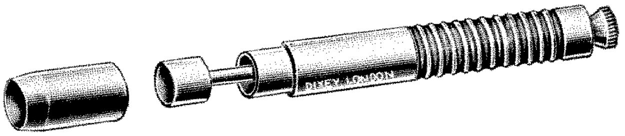

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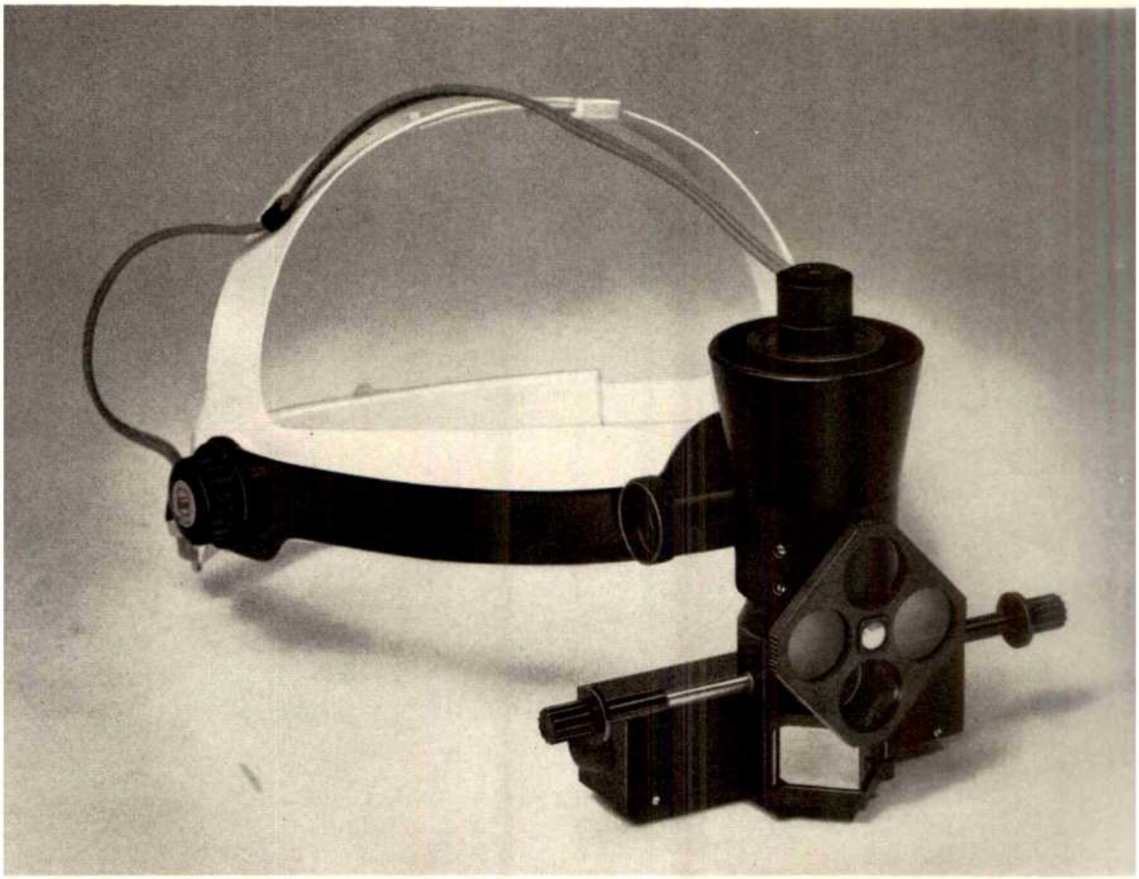

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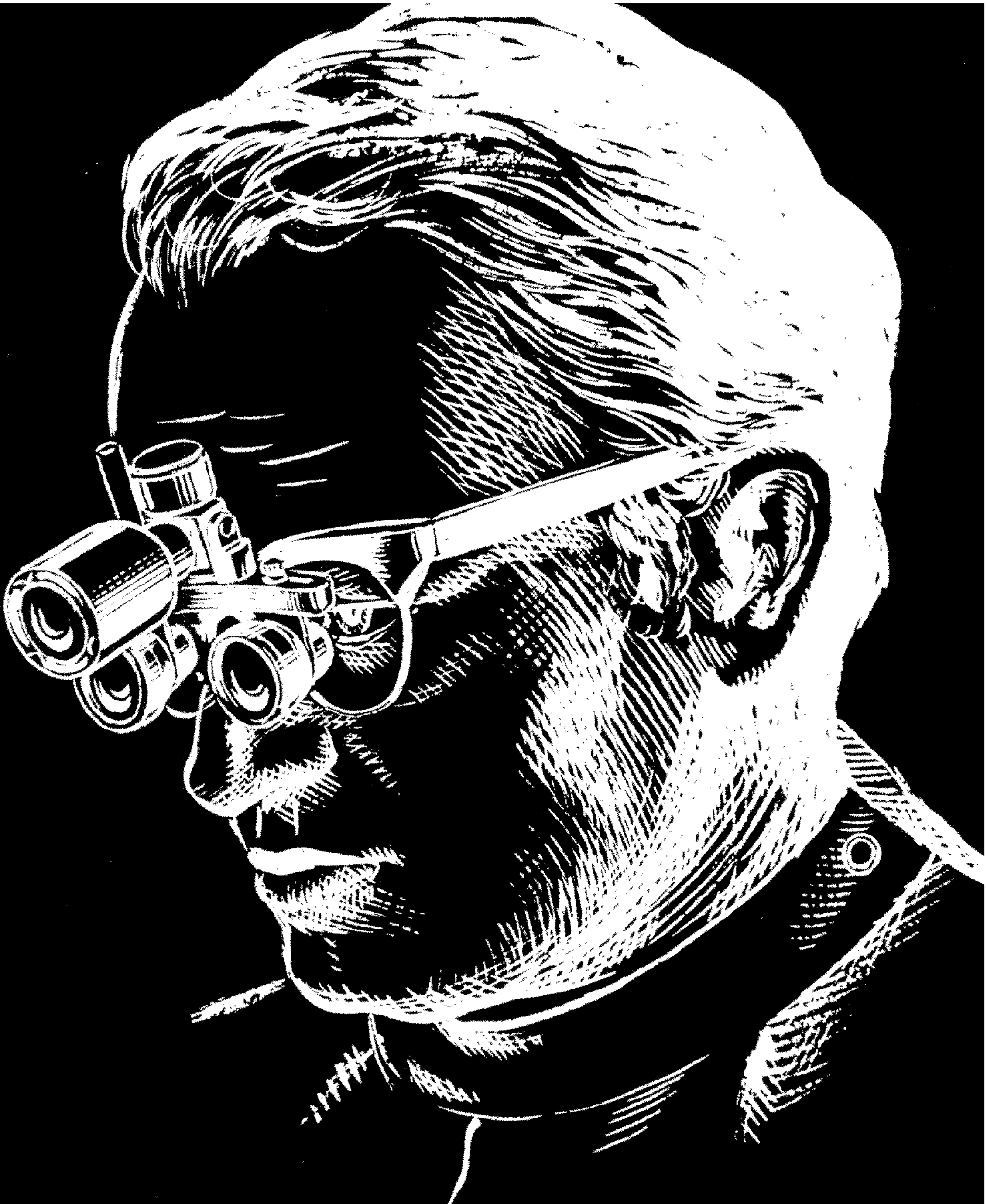

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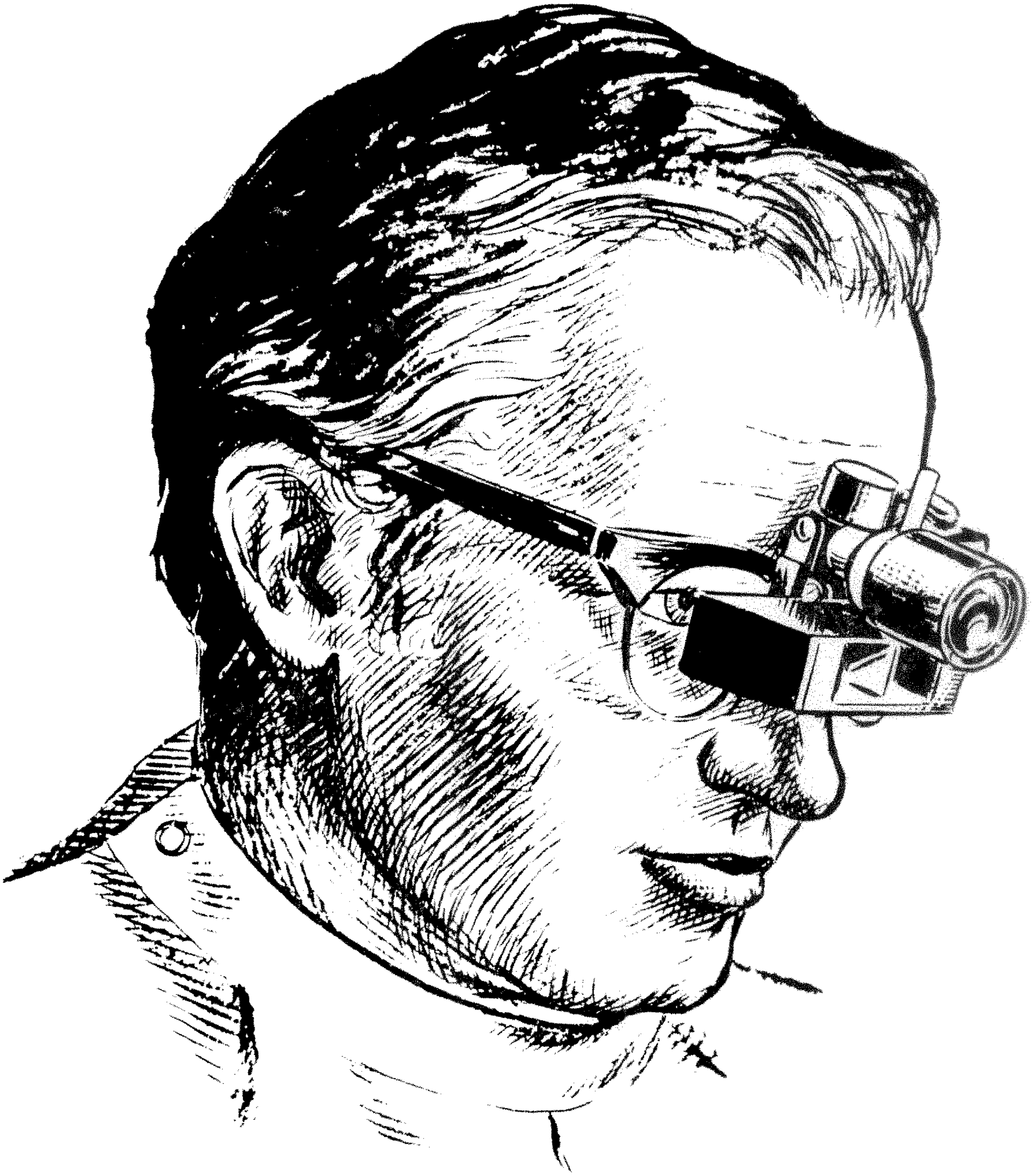

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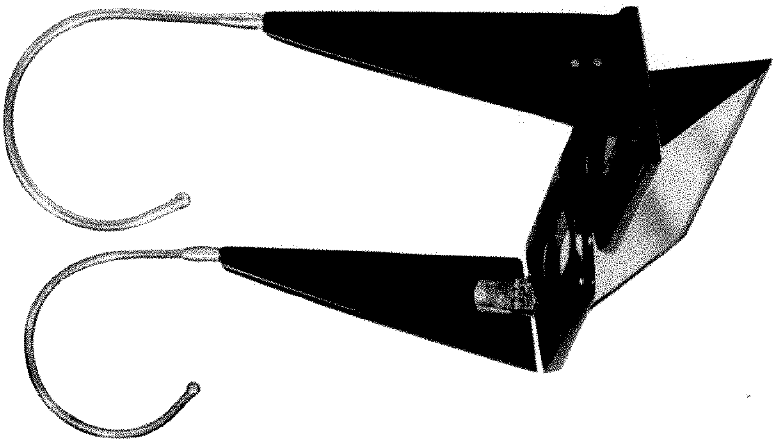

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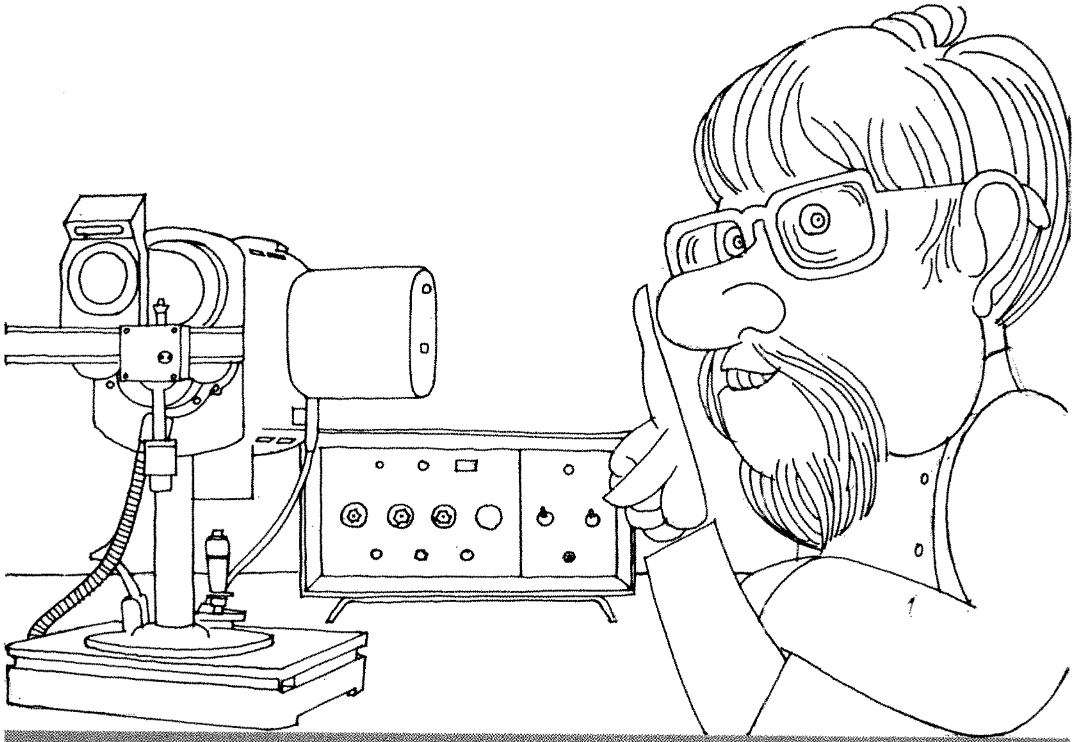

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Brit. J. Ophthal. (1971) **55**, 361

Communications

Cataract aspiration-irrigation

through separate needles with push-pull syringes

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In recent years, new methods for extracting pre-senile cataracts, particularly congenital ones, have been introduced. Two new basic principles seem to be applied (excluding the standard methods of capsulotomy, and of capsulectomy with irrigation of soft lens matter):

I. ASPIRATION ALONE Scheie (1960), Scheie, Rubinstein, and Kent (1966), Hogan (1966, 1967; Rice, 1967; and others). See also Maumenee and Ryan (1969)

II. IRRIGATION-ASPIRATION

(*a*) *Equal volumes*

  (*i*) In and out needles together: Fuchs (1952, 1962), Fink and Weinstein (1964), Atchoo (1968)

  (*ii*) In and out needles separate: None

(*b*) *Variable volumes*

  (*i*) In and out needles together: Ferguson (1964), O'Gawa (1967), Bruun-Jensen (1969)

  (*ii*) In and out needles separate: Girard (1967).

Ryan, Blanton, and von Noorden (1965) favour repeated aspiration followed by irrigation, and Middleton (1962) aspiration with intermittent filling. Harcourt and Wybar (1969) do repeated irrigation with occasional aspiration when necessary. Drews (1965) describes a special lavage needle which he uses to wash out lens matter.

Our technique fits into category II (*a*) (*ii*) in the above tabulation and differs from all the others in two ways:

(1) Using a different method of irrigation-aspiration which drives in and sucks out exactly equal volumes by means of a reciprocating push-pull arrangement

(2) Combining this with the use of separate input and output needles.

(1) Reciprocating push-pull system

Bill (1965) has devised a method for the complete mixing of solutions in the anterior

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chamber. A very similar system is used in this technique (Fig. 1). Two identical disposable syringes are arranged so that the plunger of each is fixed in positions B and D, while the barrels of each are attached to the moveable plate A. When the handle C of the apparatus is turned in one direction, the screw thread K on the central rod will cause the plate A to move so that *one syringe empties by exactly the same volume as the other syringe fills*; movement of the handle in the other direction reverses the flow. The anterior chamber maintains exactly the same depth in the absence of accidental leakage and to the observer seems remarkably undisturbed although quite large volumes of fluid are passing through it. Of course the two *syringes* must have the same diameter in order to achieve equal exchange of volume but the needles and tubing may have quite different gauges. We have tended to use two 20-ml. disposable syringes.

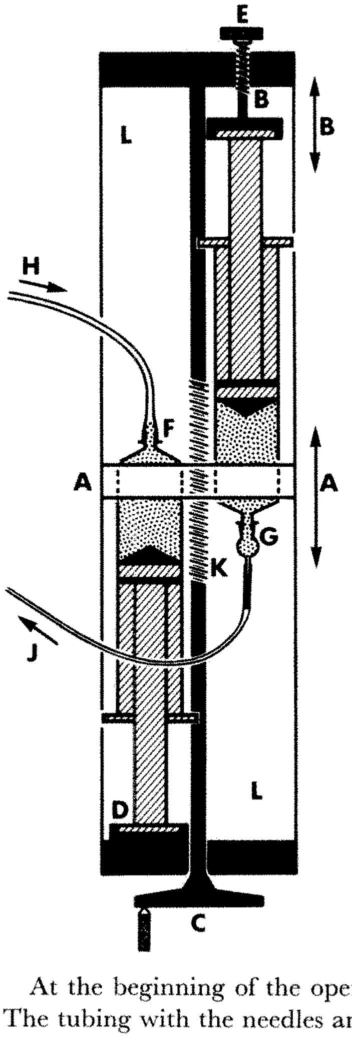

FIG. 1 *Diagram of push-pull apparatus*

A	Moveable plate with attached barrels of syringes
B	Clamp to hold plunger or irrigation syringe
C	Crank-shaft handle
D	Clamp to hold plunger of aspiration syringe
E	Screw incorporated into clamp B to give independent movement of irrigation syringe
F	Luer fitting of output cannula
G	Narrow lacrimal cannula attaching input tubing to syringe
H	Portex nylon cannula
J	Polythene input tubing
K	Screw-thread on crank-shaft
L	Base plate

When Handle C is cranked, the screw-thread K turns and moves the transverse plate AA in one direction, with the result that exactly the same volume of fluid is aspirated into one syringe as is ejected from the other. Note Screw E

At the beginning of the operation the syringes are fitted to the apparatus as in Fig. 1. The tubing with the needles and adaptors are then attached to the syringes. The system is filled with saline and all air is eliminated. The input syringe should be practically full while the receiving one should be almost empty. A separate screw E has been incorporated into the clamp holding the plunger of the input syringe so that fluid can be ejected or aspirated independently of the movement of the crank handle; accordingly, if the depth of the anterior chamber should change for any reason, it can easily be restored to normal. The heavy base plate L is useful for stability and the machine rests on a trolley near the head of the patient and is operated by an assistant. The speed of turning the crank-handle can be varied to the order of the operator who sits at the side of the patient's head.

(2) Separate input and output needles

Because security and speed of healing may be improved by the use of two separate small limbal punctures in contrast to the use of one large incision-puncture, a double needle has been avoided. The input needle can have a small gauge and we have used number 25

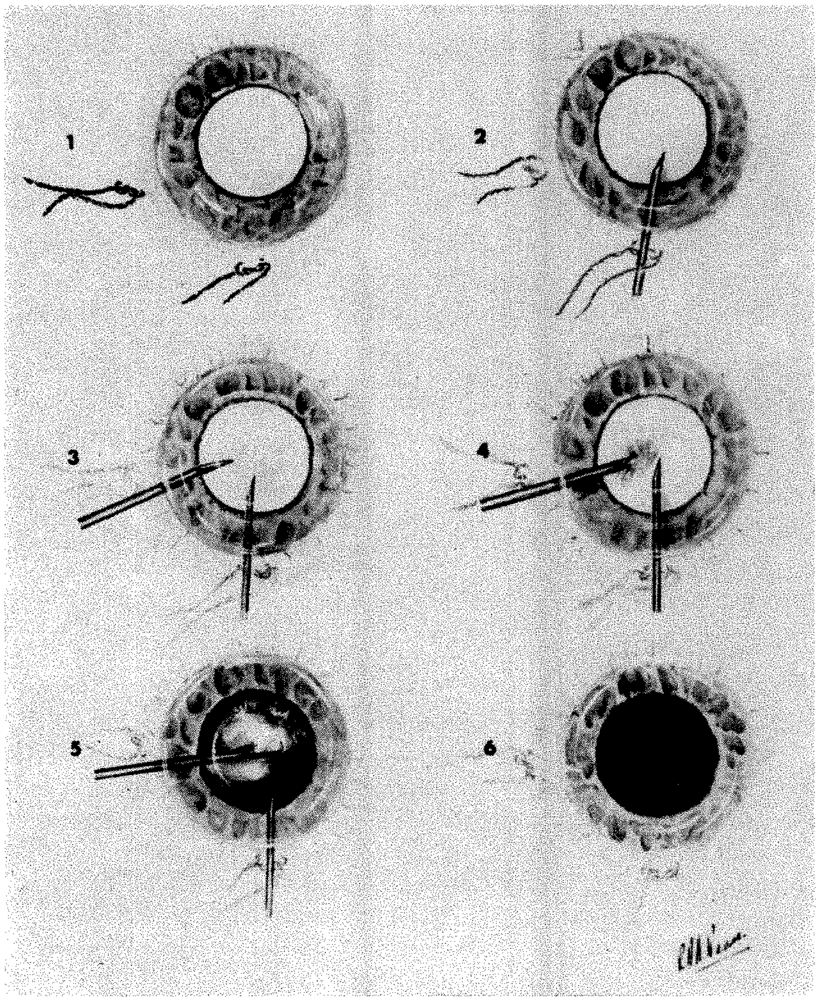

FIG. 2 *Method of aspirating/irrigating congenital and traumatic cataracts*

(1) Deep limbal fixation sutures inserted temporally and inferiorly followed by limbal scratch incisions (N.B. The sutures should be inserted at right angles to limbus, not tangentially as shown)

(2) Irrigation needle inserted inferiorly through preliminary limbal scratch incision into anterior chamber

(3) Aspiration needle inserted temporally into anterior chamber

(4) Aspiration needle passed through anterior capsule into lens substance

(5) Lens matter aspirated by push-pull

(6) Postoperative appearance

standard wire gauge. The output needle need not be large and we have found a number 23 gauge adequate. Two *deep* limbal fixation sutures are inserted inferiorly and temporally (Fig. 2.1). Tiny preliminary grooves are made into peripheral cornea with a broken razor blade or Bard-Parker No. 11 knife on one side of each fixation suture which is held with angled suture-tying forceps (Phillips, 1968). The small input needle is passed into the anterior chamber inferiorly (Fig. 2.2), while the larger output needle is inserted temporally (Fig. 2.3) and pushed through the anterior lens capsule into the lens matter (Fig. 2.4). This manoeuvre can easily be modified to produce any pattern of capsulotomy followed by disruption of lens matter as judged necessary by the state of the lens. The finger and thumb are reasonably convenient for inserting and holding these needles but purpose-designed forceps are being evolved. Each needle is directed towards the centre of the eye during penetration of the cornea, but should be parallel to the iris subsequently. There is danger of engaging iris on the point of the needle during this manoeuvre but it can be minimized if the depth of the anterior chamber is maintained by the use of the separate screw incorporated into the plunger of the input syringe. Soft lens matter is now swept into the output needle by the flow of saline from the input needle, by the turning of the crank handle (Fig. 2.5). When all possible lens matter has been removed, the output needle should be the first to be withdrawn so that the final depth of the anterior chamber can be adjusted *via* the input needle. An operating microscope facilitates the operation.

The "chop-sticks" manoeuvre

Much of the soft lens matter enters the output needle merely with the flow of saline between the two needles, and some lens matter can be "chased" into the output needle by directing the stream from the input needle. It is sometimes surprising how unwilling the lens matter is to enter the output needle; however, the input needle can be used to lever clouds of soft lens matter onto the aspiration needle. For this purpose, the axis of the input needle is best inserted at right-angles to the other. Girard (1967) has described a similar method. It is probably best to carry out this technique while flow is temporarily stopped, as this economizes in fluid.

Technique for making needle-tubing combination

The input needle has a No. 25 gauge and the output needle a No. 23 gauge; they are "disposable". In order to remove the steel needle stem from the plastic Luer end, each is grasped firmly but not tightly with pliers (Fig. 3). An assistant applies the flame of a match or cigarette lighter to the area where the plastic fitting joins the steel needle and the latter is pulled away. The blunt end of the No. 23 gauge output needle is inserted into the distal end of a Portex nylon intravenous cannula of diameter 1·34 mm. and length 30 in., and tied with silk or terylene. The advantage in using the Portex cannula is that the proximal end is a Luer fitting which can be immediately attached to the output syringe.

The blunt end of the 25 gauge input needle is inserted into one end of a 30 in. length of polythene tubing, internal diameter 0·50 mm., and tied. A narrow lacrimal cannula is inserted into the other end of the polythene tubing and this is attached to the input or injection syringe. Saline is therefore injected from the input syringe into the anterior chamber *via* the lacrimal cannula, the polythene tubing, and the input needle.

The push-pull machine and Portex nylon cannula can be autoclaved but the polythene tubing cannot be so sterilized. Polythene tubing with the attached needles should preferably be sterilized by gamma-radiation. As a secondary method it *can* be boiled, BUT no pressure should be applied during this process or while the tubing is hot as this will cause distortion.

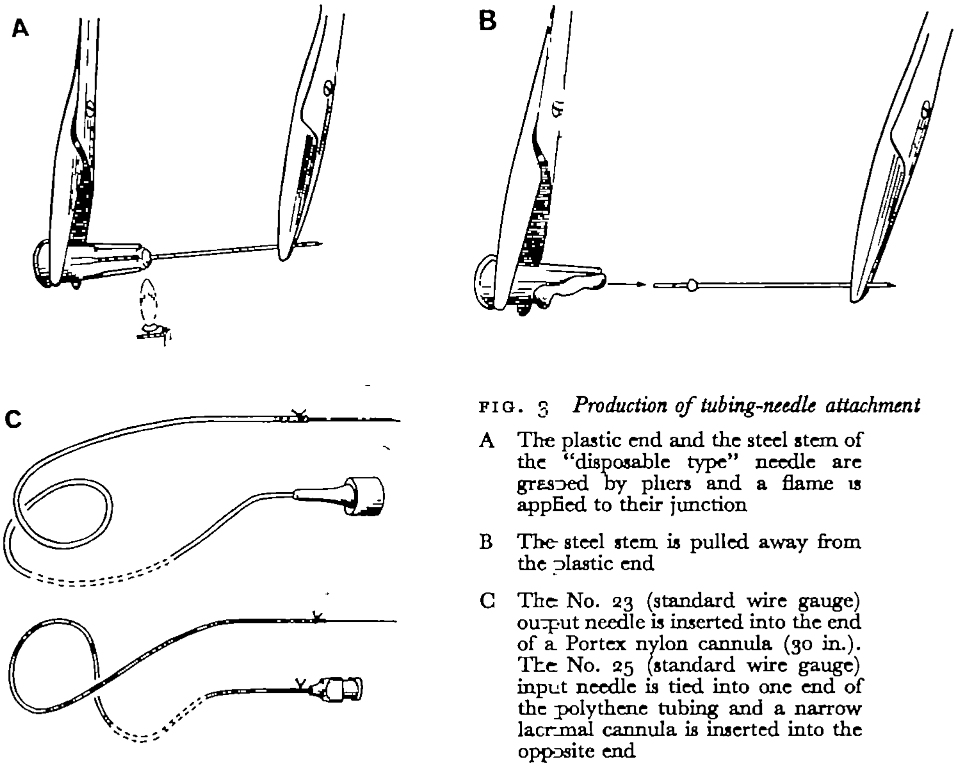

FIG. 3 *Production of tubing-needle attachment*

A The plastic end and the steel stem of the "disposable type" needle are grasped by pliers and a flame is applied to their junction

B The steel stem is pulled away from the plastic end

C The No. 23 (standard wire gauge) output needle is inserted into the end of a Portex nylon cannula (30 in.). The No. 25 (standard wire gauge) input needle is tied into one end of the polythene tubing and a narrow lacrimal cannula is inserted into the opposite end

Discussion

With some practice the method described has been found fairly easy to use, safe, and superior to other methods we have used in congenital and traumatic cataracts. We have done fifteen operations so far, after some experiments on rabbit and eye-bank eyes. Only one operation has been regarded as a failure—the unexpected hardness of some parts of a traumatic cataract in a man of 56 years defeated the technique, but conversion to an ordinary extracapsular operation through a small limbal incision was fairly easy. The patients have all had quiet eyes and have been discharged from hospital sooner than usual.

The main disadvantage of a technique of aspiration alone would seem to be the hypotensive distorted eye even if only transient. It seems reasonable to suggest that the addition of an inflow needle with physiological saline has so few disadvantages that they must be far outweighed by the advantages.

Two separate operations, one for capsulotomy followed by one for aspiration and/or irrigation, are a serious imposition, especially in a young child, in spite of modern techniques of anaesthesia. A major advantage of this procedure is that the number of anaesthetics is reduced usually to one because capsulotomy is part of the initial stage in the operation; occasionally a supplementary posterior capsulotomy may be necessary.

Probably a defect in the above method is the absence of an iridectomy. However, this could be done at the end of the aspiration-irrigation. It may be feasible to perform an iridotomy (without iridodialysis) with the point of one of the needles, or the points of both may be used to achieve a sphincterotomy or sphincterotomies. With the present method of inserting the needles, it would be difficult to fashion a pupil by the Franceschetti corepraxy as discussed by Maumenee and Goldberg (1965).

A satisfactory sector iridectomy would aid the full examination of the retina in the long-term future, when retinal detachment may occur. Chandler (1968) has described good results from the classical extracapsular type of operation and it may be that this well-tried method should remain standard; however, there is probably more potential danger of serious complications than with the method described here—subject to the assessment of a larger series of cases over a longer period than we have done so far.

Some distortion of the lens-suspensory ligament by these manoeuvres is still unavoidable, but it is probably less than in other types of operation. It may well be possible to insert the needles through the cornea with a cannula gun such as that described by Sears (1960).

Possible future developments

Kelman (1967) has described an ultrasonic vibrating probe to disintegrate sclerotic lens matter. An attempt is being made to incorporate a microdrill, preferably rotating at ultrasonic speeds, into our present push-pull apparatus to break up cataracts of the senile type (Phillips, Wang, and Pullan, 1970). Another possible method for applying the aspiration-irrigation principle to senile cataracts would be to add the microexplosion produced by a spark gap (see Watson, 1970).

Summary

A reciprocating push-pull system (see Fig. 1) can achieve exactly equal volumes for irrigation and aspiration of congenital or traumatic cataracts. The two syringes must be identical (*e.g.* disposable 20 ml.). The machine lies on a trolley and is operated by an assistant.

Separate input and output needles, 25 and 23 standard wire gauge respectively, are used. The connection between the irrigating 25 gauge needle and syringe is made by polythene tubing while that between the aspirating 23 gauge needle and syringe is made by a Portex nylon intravenous cannula (30 in.). Disposable needles are detached from their plastic Luer ends by means of heating in a match flame and easily tied into the end of the tubing. The polythene tubing is fed over a lacrimal cannula which in turn is pushed firmly onto the nozzle of the input syringe while the Portex nylon cannula has a Luer end which can be attached directly onto the output syringe.

The advantages of this method as observed in fifteen patients so far treated are:

(*a*) Safety in that a more "open" operation is avoided

(*b*) Only one definitive anaesthetic and operation is required

(*c*) Speedy convalescence and "quiet" eyes with early discharge from hospital.

The main disadvantage may be the absence of a sector iridectomy.

The authors are grateful to Mr. J. W. Flowett and Mr. G. A. Needham, of the Department of Mechanical Engineering at the University of Manchester Institute of Science and Technology, for making the machines, and to Mr. A. Lymer, of the Supplies Department, Manchester Royal Infirmary, for devising the attachment of the needles to the tubing.

They also thank Mr. R. A. H. Neave and Mr. K. Harrison of the Department of Medical Illustration, Manchester Royal Infirmary, for artistic help.

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Addendum

It is possible, especially when first using the push-pull machine, that the operator may use up the saline before all the lens matter has been irrigated-aspirated. A plastic 3-way stopcock (K75 by Pharmaseal Laboratories, Glendale, California 91201) between the nozzle of each syringe and its tubing allows the syringes to be isolated from the eye and emptied (in the case of the recipient) or re-filled (in the case of the donor) if neccesary.

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Rubeosis of the iris and haemorrhagic glaucoma in patients with proliferative diabetic retinopathy

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Although abnormal iris vessels and secondary glaucoma in a patient with proliferative diabetic retinopathy was described over 80 years ago by Nettleship (1888), Salus (1928) was the first to call attention to rubeosis of the iris as a specific manifestation of long-term diabetes and to point out that the neovascularization of the iris resulted in haemorrhagic glaucoma.

Neovascularization of the iris and the chamber angle is far less frequent than retinal changes in diabetics. In nonselected groups of diabetics, rubeosis of the iris occurs in only a small percentage (Ohrt, 1958; Armaly and Baloglou, 1967). Most frequently, the iridic neovascularization appears in eyes with proliferative retinopathy (Janert, Mohnike, and Georgi, 1957; Krüger, 1961; Ohrt, 1967; Madsen, 1971a).

The purpose of this paper is to describe the occurrence of rubeosis of the iris and the development of this affection in diabetics with proliferative retinopathy.

Material

The series consists of 68 diabetics suffering from proliferative retinopathy. These patients were examined repeatedly during the years 1963–1968 in the Departments of Ophthalmology and Internal Medicine, the University Hospital, Aarhus. The examination was carried out by means of a slit lamp, often with great magnification, and red-free light. The site of the neovascularization was described in detail, in many cases accompanied by drawings for subsequent comparison.

Proliferative retinopathy had been present for years in most of the patients before the appearance of the rubeosis.

Hypophysectomy had been carried out in 31 of the patients. Further information on the 68 patients is given in the following paper (Madsen, 1971b).

Results

Rubeosis of the iris was seen in 58 eyes during the observation period. One of the eyes was removed on account of haemorrhagic glaucoma. At the last examination, rubeosis of the iris was observed in 42 eyes, but had disappeared in fifteen eyes (Table I, opposite).

In many patients, rubeosis of the iris may be unchanged for several years, or there may be fluctuation in the severity of the neovascularization. In nineteen patients, rubeosis of the iris had repeatedly been observed in 24 eyes without being followed by haemorrhagic glaucoma during the observation period. As shown in Table II, the observation time was up to 5 years.

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Table I *Occurrence of rubeosis of the iris and haemorrhagic glaucoma in 135 eyes (last examination)*

Rubeosis of the iris	*Hypophysectomy*		*Total*
	Performed	*Not performed*	
0	44	49	93
(+)	5	2	7
+	8	12	20
++	5	10	15
Rubeosis previously observed	4	11	15
Haemorrhagic glaucoma	5	8	13

Stages:	
0	No rubeosis
(+)	Small vascular coils at pupillary border
+	Greater vascular networks in annulus minor
++	Severe rubeosis with vessels on entire iris surface

Table II *Rubeosis of the iris in 28 eyes without haemorrhagic glaucoma*

Age (yrs)	*Sex*	*Eye*	*Time of observation (mths)*	*Rubeosis of the iris*	*Chamber angle*	*Hypophysectomy*
45	F	R	39	(+)	—	+
		L	39	(+)	—	+
30	F	R	11	(+) → +	?	+
30	M	R	7	(+) → +	—	+
64	M	R	64	+	—	+
56	M	R	44	+	— → o.v.	+
44	F	R	50	(+)	—	+
		L	50	+	—	+
32	M	L	35	+ → (+)	—	+
37	F	R	60	(+) → +	—	
38	M	L	48	+	—	
37	F	L	7	+	—	
40	F	R	37	+ → ++ → +	—	
		L	37	+ → ++ → +	—	
34	M	R	4	(+)	—	
23	F	R	23	+ → ++ → +	— → o.v.	
		L	11	—	o.v.	
49	M	L	25	(+) → +	—	
59	F	R	38	+	—	
44	M	R	17	+ → (+)	—	
60	M	R	31	+ → ++	o.v.	
65	M	R	9	+ → ++	o.v.	
		L	9	+	o.v.	
36	M	L	38	++ → +	o.v.	

Key to abbreviations: o. = open angle v. = new-formed vessels in angle

Rubeosis of the iris occurred with almost the same frequency in hypophysectomized and nonhypophysectomized patients, as did the other signs of diabetic iridopathy, *viz.* porosity and atrophy of the pupillary border, atrophy of the iris, and deposits of pigment granules on the surface of the iris.

Haemorrhagic glaucoma occurred in fourteen eyes during the observation period. In our eyes, glaucoma was already present at the first examination; in ten eyes rubeosis of the iris was observed before the onset of haemorrhagic glaucoma. Table III shows the time interval between the appearance of rubeosis of the iris and the onset of the haemorrhagic glaucoma. This interval varied from 1 to 38 months.

Table III *Time interval between detection of rubeosis iridis and occurrence of haemorrhagic glaucoma*

Age (yrs)	*Sex*	*Eye*	*Interval (mths)*	*Development of rubeosis of the iris*	*Chamber angle*	*Hypophysectomy*
29	F	L	1	+ → ++	o.v. → cl.	+
32	M	R	12	+ → ++	— → cl.	+
37	F	L	36	+ → ++	— → o.v.	+
32	M	R	27	+ → ++	o.v. → cl.v.	
		L	32	+ → ++	— → cl.v.	
27	F	R	6	+ → ++	— → cl.v.	
30	M	R	1	+ → ++	— → o.v.	
49	M	R	13	+ → ++	o.v. → o.v.syn.	
59	F	L	38	+ → ++	? → cl.	
44	M	L	17	++	? → cl.	

Key to abbreviations: o. = open angle; cl. = closed angle; v. = new-formed vessels in angle; syn. = synechiae

Simple glaucoma was seen in only one patient (hypophysectomized). Otherwise, the intraocular pressure was low in the great majority of the patients in this series. At the last examination, the average intraocular pressure in 54 nonglaucomatous eyes in the hypophysectomized patients was 12·5 mm. Hg, and in 61 eyes in the nonoperated patients the average was 13·3 mm. Hg.

Very low intraocular pressures were found in eyes in which haemorrhagic glaucoma later developed. In eight of the ten eyes in Table III, intraocular pressures of 10 mm. Hg or less (applanation) were found in the period before the occurrence of the glaucoma. In this hypotonic phase, rubeosis of the iris developed, followed by a rise in the intraocular pressure, of sudden or more gradual onset. Such a case with hypotonia and subsequent development of haemorrhagic glaucoma is shown in the figure.

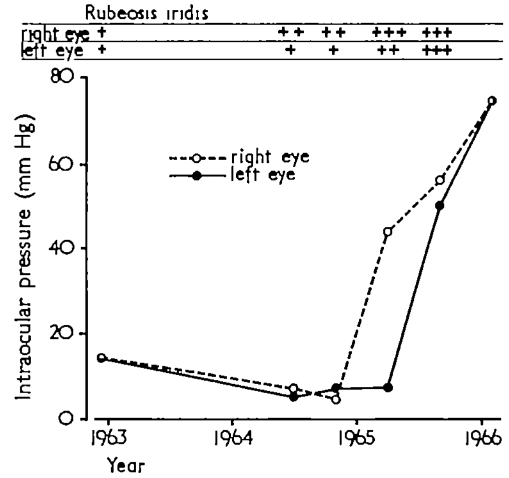

FIGURE *Intraocular pressure and development of rubeosis iridis in a young man with proliferative diabetic retinopathy in both eyes*

Discussion

Rubeosis of the iris is relatively frequent in eyes with proliferative diabetic retinopathy, and occurred in 43 per cent. in the present series. It is a serious complication on account of the frequent concomitant occurrence of haemorrhagic glaucoma. This form of glaucoma supervened in fourteen of the 58 eyes with iridic neovascularization during the observation period.

It is shown that, in some eyes, rubeosis of the iris may run a very slow course. There may be periods of exacerbation or regression, or the new-formed iridic vessels may eventually disappear, as has also been demonstrated in other series (Ohrt, 1967). In all cases under observation, haemorrhagic glaucoma occurred after the development of neovascularization in the iris and chamber angle. No case of secondary rubeosis was seen.

Hypotonia seems to be an important factor in the development of rubeosis of the iris and the subsequent haemorrhagic glaucoma.

Summary

In a series of 68 patients with proliferative diabetic retinopathy, rubeosis of the iris was observed in 58 eyes, including 22 in patients who had been subjected to hypophysectomy during an observation period of up to 5 years. Haemorrhagic glaucoma occurred in fourteen eyes.

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Prognosis for vision and fundus changes in patients with proliferative diabetic retinopathy

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Diabetic retinopathy has become one of the major causes of adult blindness in many countries (Winter, 1960; Vedel-Jensen, 1962; Caird and Garrett, 1963; Lee, McMeel, Schepens, and Field, 1966; Caird, Burditt, and Draper, 1968; Caird, Pirie, and Ramsell, 1969; Lindstedt, 1969). Proliferative retinopathy is the severest form of the diabetic fundus disease, and although it occurs in only a small percentage of the patients in a non-selected diabetic population, proliferative retinopathy is particularly feared, as it is often followed by rapid loss of vision. Drastic therapeutic measures, such as photocoagulation, hypophysectomy, and adrenalectomy, have been applied in an attempt to stop the progression of this late diabetic manifestation.

The purpose of the present paper is to describe the development of the fundus changes and to give an impression of the visual prognosis in diabetics with proliferative retinopathy.

Material

The series consists of 68 patients (38 men and 30 women) with proliferative diabetic retinopathy from the Departments of Ophthalmology and Internal Medicine, the University Hospital, Aarhus. The patients were examined repeatedly by the author during the 5-year period 1963–68, and the retinal lesions were repeatedly recorded by fundus drawings and photographs. In many of the patients, proliferative retinopathy had been diagnosed before 1963, and the results of these early observations were incorporated in the present study.

Hypophysectomy had been performed in 31 patients (62 eyes). The length of the observation period appears from Fig. 1. The patients submitted to hypophysectomy were observed for 12 to 131 months (mean 58; S.D. 23·5), while the nonoperated patients were observed for 7 to 89 months

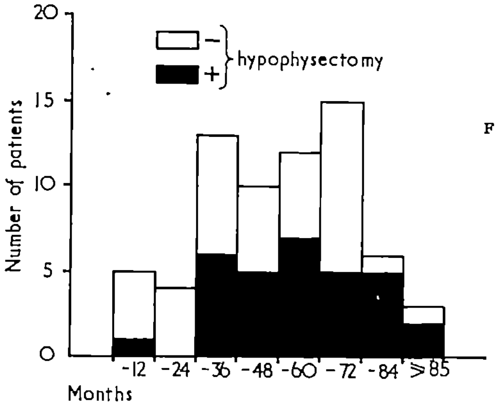

FIG. 1 *Length of observation period*

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(mean 43; S.D. 21·8). Even though the observation time is longer in the hypophysectomized group and despite a slight predominance of old patients in the nonoperated group, it seems justified to make a certain comparison between the hypophysectomized and nonhypophysectomized patients. Reports on the hypophysectomized patients were previously published by Lundbaek, Malmros, Andersen, Rasmussen, Bruntse, Madsen, and Jensen (1969) and Madsen (1970).

General data

The following presentation of general data is based on the findings at the last examination.

The age distribution is shown in Table I; 75 per cent. of the patients were under 50 years.

The duration of diabetes is shown in Table II; 84 per cent. had had diabetes for 20 years or more.

Table I *Age distribution of* 68 *patients*

Age (yrs)	*Hypophysectomy* *Performed*	*Hypophysectomy* *Not performed*	*Total*
20–29	4	4	8
30–39	15	16	31
40–49	6	6	12
50–59	5	5	10
60–69	1	5	6
70–		1	1
Total	31	37	68
Mean	38·8	43·4	
Standard deviation	9·34	9·37	
Range	26–64	23–81	

Table II *Duration of diabetes in* 68 *patients*

Duration (yrs)	*Hypophysectomy* *Performed*	*Hypophysectomy* *Not performed*	*Total*
0– 9		1	1
10–19	4	6	10
20–29	19	20	39
30–	8	10	18
Total	31	37	68
Mean	26·4	24·6	
Standard deviation	6·44	7·22	
Range	12–45	6–38	

The patients' ages at the time of diagnosis of diabetes is shown in Table III; 75 per cent. were under 20 years when diabetes was diagnosed.

Table III *Age at which diabetes was diagnosed in* 68 *patients*

Age at diagnosis (yrs)	*Hypophysectomy* *Performed*	*Hypophysectomy* *Not performed*	*Total*
0–9	17	10	27
10–19	8	16	24
20–29	3	2	5
30–39	2	4	6
40–49	1	2	3
50–59		3	3
Total	31	37	68
Mean	12·5	18·8	
Standard deviation	9·22	15·79	
Range	1–40	1–59	

The occurrence of proteinuria, increased serum creatinine values, and arterial hypertension is listed in Table IV (overleaf): 60 per cent. had proteinuria; 19 per cent. had serum creatine values above 1·3 mg./100 ml.; 40 per cent. a blood pressure above 150/100 mm. Hg (Lundbaek, 1953); and 20 per cent. a diastolic pressure above 100 mm. Hg.

Table IV *Proteinuria, serum creatinine, and blood pressure*

Test		*Hypophysectomy*		*Total*
		Performed	*Not performed*	
Proteinuria	Absent	9	18	27
	Present	22	18	40
Serum creatinine (mg. per cent.)	> 1·3	24	26	50
	⩽ 1·3	7	5	12
Blood pressure (mm. Hg)	⩽ 150/100	20	18	38
	> 150/100	11	14	25
	Diastolic pressure > 100	4	8	12

The treatment is shown in Table V. Insulin was given in all but two patients. After hypophysectomy the insulin requirements fell to about one half of the preoperative dose, which explains the low dosage of insulin in the group subjected to hypophysectomy.

Table V *Treatment of* 68 *patients with diabetes*

Treatment	*Hypophysectomy*		*Total*
	Performed	*Not performed*	
Diet		1	1
Oral antidiabetic drug		1	1
Insulin — 40 I.U.	27	21	48
> 40 I.U.	4	14	18
Total	31	37	68

Table VI *Average visual efficiency in individual eyes (per cent.)*

Examination	*Hypophysectomy*	
	Performed	*Not performed*
First	55	58
Last	47	40

Ocular data

VISUAL ACUITY

Fig. 2 shows the visual acuity in the 136 individual eyes of the 68 patients at the first and last examinations.

During the period of observation, a fall in visual acuity to less than 0·1 was seen in 22 eyes (10 in hypophysectomized and 12 in nonhypophysectomized patients). The loss of vision occurred during the first year in two of the patients subjected to operation, but in six in the nonoperated group. During the second year, two eyes in both groups lost vision, whereas blindness did not occur until after 2 years in six and four eyes, respectively.

Visual improvement from less than 0·1 to more than 0·1 was observed in four eyes (three in hypophysectomized patients).

Fig. 3 shows the visual acuity in the patient's best eye at the first and last examinations; it is seen that four patients were blind (visual acuity less than 0·1 in both eyes) at the first examination, but eleven were blind at the last check-up. Ten of these eleven blind patients were under 50 years and had had diabetes since before the age of 20 years.

If visual efficiency (Snell and Sterling, 1925) is used instead of visual acuity in the assessment of vision in the individual eyes in the two groups, the averages obtained are those given in Table VI. It is seen that the decrease in vision was fairly moderate in both groups, *viz.* 8 per cent. in the hypophysectomized and 18 per cent. in the nonhypophysectomized patients.

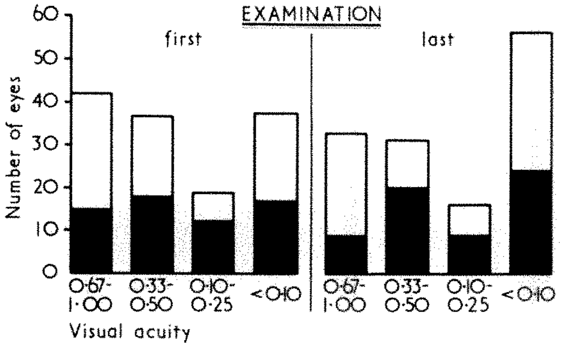

FIG. 2 *Visual acuity in individual eyes*

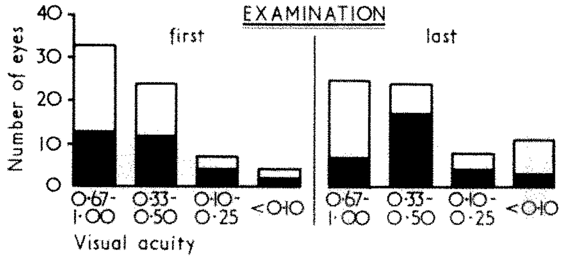

FIG. 3 *Visual acuity in patients (vision of best eye)*

RETINOPATHY

Background retinopathy

This was very frequent in both groups of patients.

Severe arterial changes seemed to be more frequent in the hypophysectomized patients, and the phlebopathy was somewhat more pronounced in the nonoperated patients.

Red dots, haemorrhages, and exudates were numerous in patients suffering from proliferative retinopathy in the first stages. As the proliferative retinopathy developed, with formation of connective tissue and vitreous detachment, the background retinopathy tended to decrease.

After hypophysectomy an unmistakable improvement in the background retinopathy was observed. Most of the red dots and haemorrhages disappeared, the phlebopathy abated, and the hard exudates decreased in number. An example of this development is shown in Figs 4 and 5. After some years, red dots and haemorrhages reappeared in many of the hypophysectomized patients, but they were less numerous than before the operation.

Proliferative retinopathy

This differed widely, not only from patient to patient, but also in the two eyes of the individual patient. The development of the proliferations seemed to follow a certain pattern. They often started as fine vessels either on the disc or on the retina outside the disc area. Then the vessels gradually spread, and connective tissue appeared around the central part of the vessels, while the peripheral networks or coils were still naked. At first the connective tissue was thin and veil-like, but it gradually became denser, although the development was still dominated by the vascular proliferations. Then some vessels

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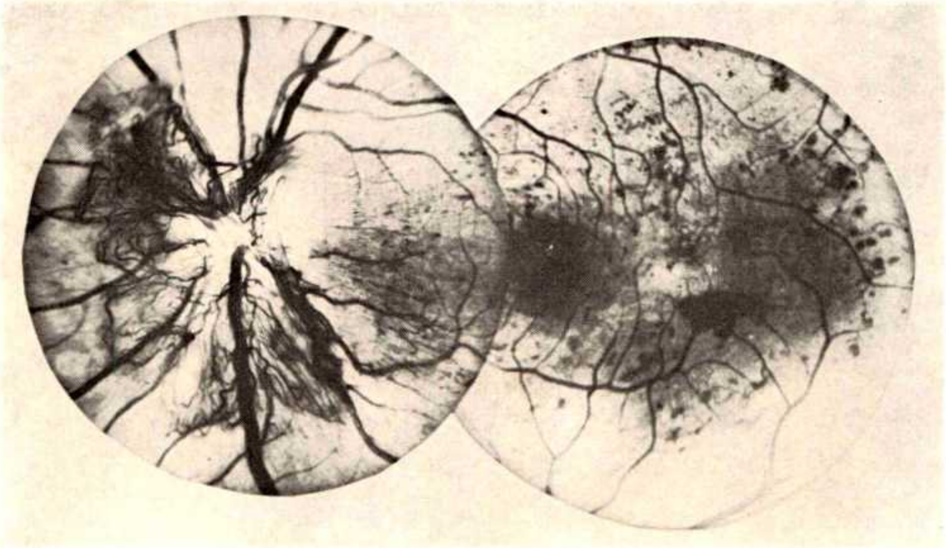

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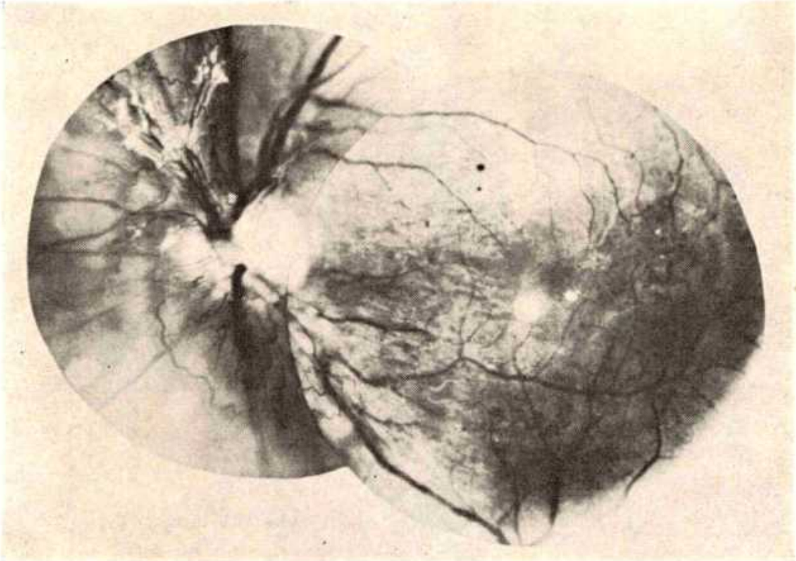

FIG. 4 *Left fundus in a woman aged 30 (before hypophysectomy)*

FIG. 5 *Same eye as in Fig. 4, 12 months later (11 months after hypophysectomy)*

disappeared, and the progressive phase was followed by regression. The connective tissue shrank with ensuing traction on the retina and the retinal vessels.

As a rule, the development of the proliferative retinopathy was most progressive when the changes were localized in the disc area, and it was most severe in eyes with large retrovitreal haemorrhages (Figs 6 and 7, opposite). When the eyes had reached the stage of regression, their condition might remain unchanged for several years.

Fig. 8 (overleaf) shows the occurrence of proliferative retinopathy in individual eyes in different stages (Dobree, 1964). At the first examination, proliferations consisting of naked vessels (Stage I) were seen in 38 per cent. of all eyes and connective-tissue proliferations (Stages II and III) in 48 per cent. At the last examination, naked vessels were present in 22 per cent. of the eyes and connective tissue in 51 per cent. The fundus could not be

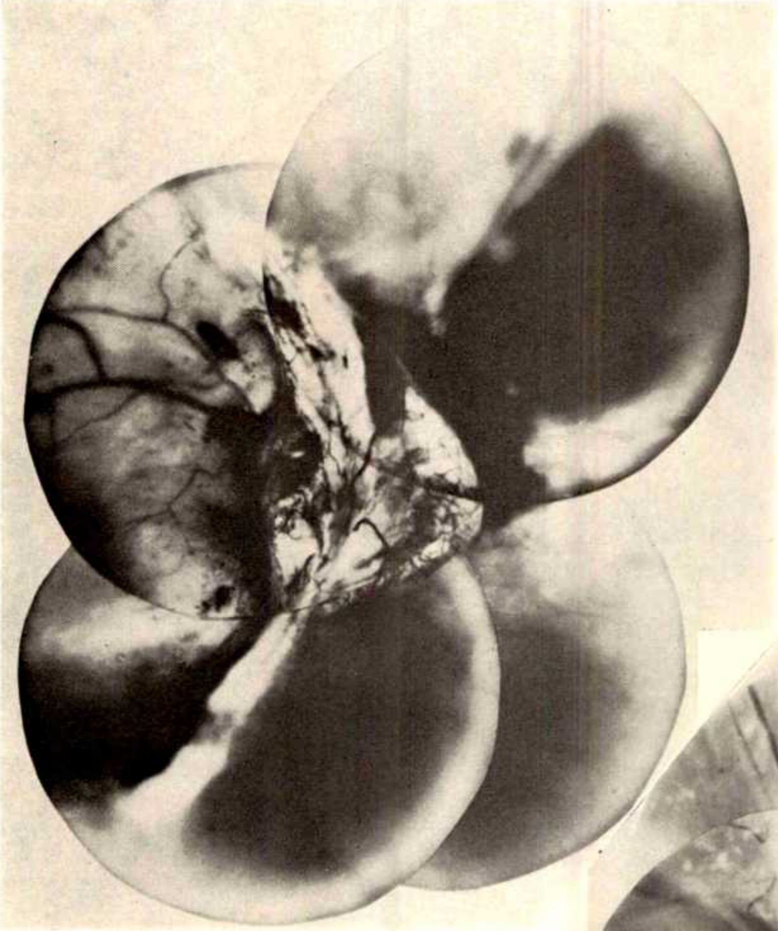

FIG. 6 *Right fundus in a woman aged 31, with extensive vascular and connective tissue proliferations and retrovitreal haemorrhages*

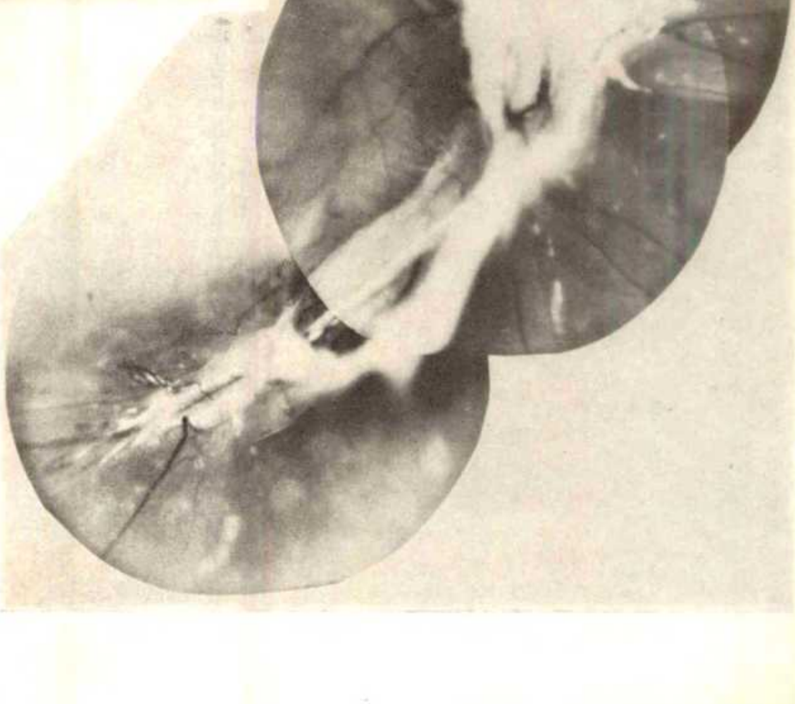

FIG. 7 *Same eye as in Fig. 6, 32 months later. Contracture of connective tissue; most of the vessels have disappeared, but almost complete detachment of the retina due to traction has occurred*

examined on account of cataract, vitreous haemorrhage, or haemorrhagic glaucoma in 6 per cent. of eyes at the first, and 18 per cent. at the last examination. The severest cases of proliferative retinopathy in the entire series are to be found in this group.

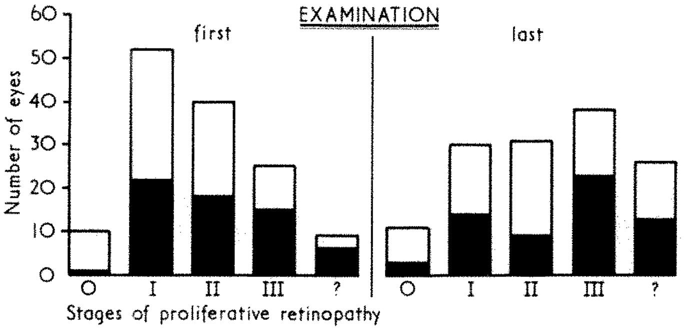

FIG. 8 *Stages of proliferative retinopathy:*

o	No proliferations
I	Naked vessels
II	Connective tissue and dense vascular proliferation (active stage)
III	Dense connective tissue with contracture, decrease in vascular system (stage of regression)
?	Fundus could not be seen

The localization of the proliferations is shown in Fig. 9. Both the first and the last examinations revealed proliferations on both the disc and retina in the vast majority of the eyes. It should be noted that localized prepapillary proliferations became more severe in all the nonoperated patients.

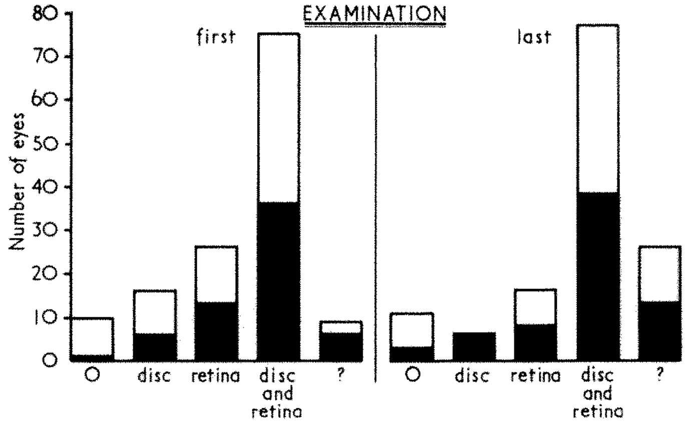

FIG. 9 *Localization of proliferative retinopathy*

The course of the proliferative retinopathy in the various stages is given in Table VII (opposite). Unchanged conditions or even improvement were seen in 47 per cent. of the eyes, whereas progression—especially in Stage II—was noted in 46 per cent. of the eyes (Figs 6, 7, 10, 11). Severe progression seemed to be more frequent in the nonhypophysectomized group.

The causes of the progression in 63 eyes are given in Table VIII (opposite). In more than half of the eyes, the deterioration was due to retrovitreal haemorrhages followed by connective tissue formation and, in some cases, also by detachment of the retina due to traction. No difference in the occurrence of these changes was observed in hypophysectomized and nonhypophysectomized patients.

Progression exclusively in the form of new naked vessels was seen in 8 per cent. of eyes, and development of connective tissue in 30 per cent. Table VIII shows a distinct difference between the operated and nonoperated patients as the development of vessels

Table VII *Course of proliferative retinopathy in 136 eyes in 68 patients*

Hypophysectomy	*Stage at first examination*	*Course* *No change*	*Improvement*	*Progression*	*Severe progression*	*?*
Performed	0	1	0	0	0	
	I	10	4	6	2	
	II	4	2	2	10	
	III	9	0	1	5	
	?					6
	Total (62 eyes)	24	6	9	17	6
Not performed	0	7	0	1	1	
	I	10	4	1	15	
	II	3	1	4	14	
	III	9	0	0	1	
	?					3
	Total (74 eyes)	29	5	6	31	3
Total	136 eyes	53	11	15	48	9

Stages as in Fig. 8

Table VIII *Causes of progression in proliferative retinopathy in 63 eyes*

Cause	*Hypophysectomy* *Performed*	*Not performed*	*Total*
Retrovitreal haem. + vascular and conn. tissue proliferation	12	12	24
Retrovitreal haem. + vessels and conn. tissue + detachment of retina	6	4	10
Naked vessels	2	3	5
Vessels and conn. tissue	4	15	19
Vessels, conn. tissue + detachment of retina	0	3	3
Detachment of retina without new proliferations	2	0	2
Total	26	37	63

Table IX *Eyes with arrest in proliferative diabetic retinopathy—assessed at different stages (number of eyes)*

Hypophysectomy	*Stage at first examination*	*Duration of observation period (mths)* −12	−24	−36	−48	−60	−72	−84	≥85	*Total*
Performed	0					1				1
	I	2		3	5	1	2		1	14
	II			1		1	1	3		6
	III			1	2		3	3		9
Not performed	0			1	1		4		1	7
	I			3	1	2	7		1	14
	II	1	1		1		1			4
	III	1		1			7			9
Total		4	1	10	10	5	25	6	3	64

and connective tissue without preceding retrovitreal haemorrhage predominated in the nonoperated group.

Table IX shows the observation period for 64 eyes with arrest or improvement in the development of the proliferations. The Table includes eight eyes in which no proliferations were seen during the entire period. Most of the patients were under observation for several years, and it appears that unchanged conditions were observed in many patients who had not been subjected to hypophysectomy.

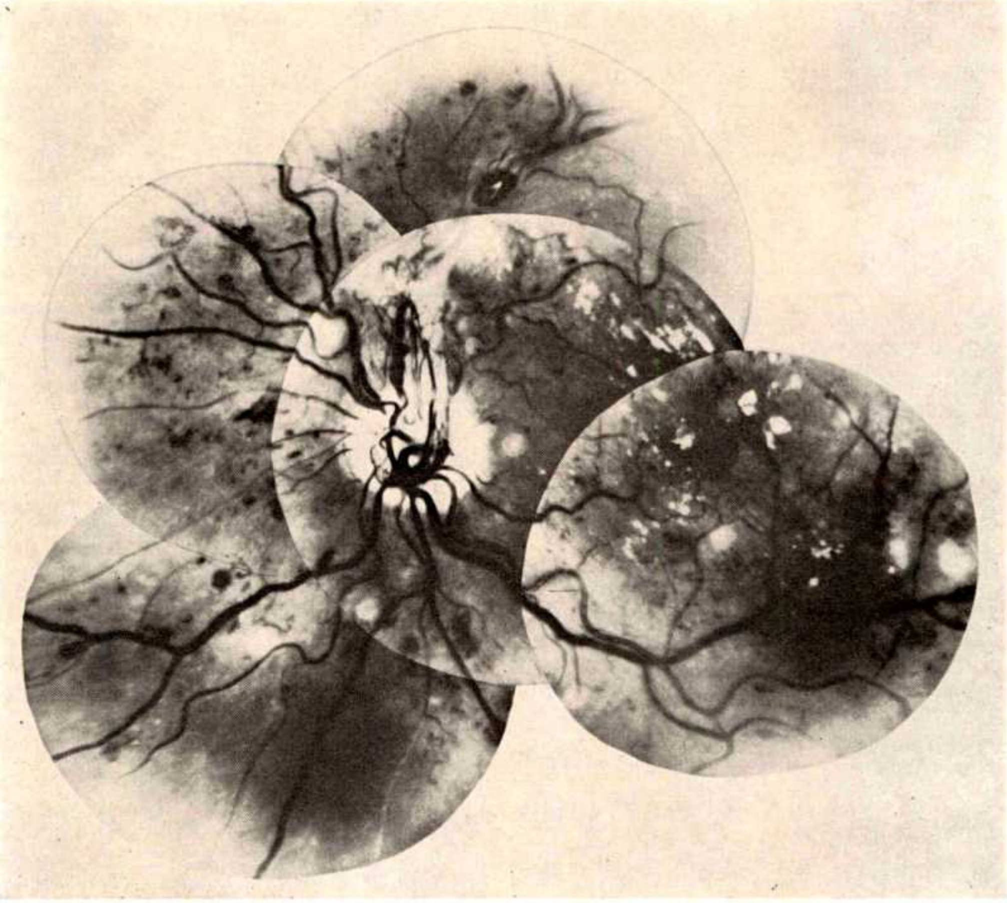

FIG. 10 *Left fundus in a man aged 46. Vascular proliferations and veils of connective tissue. Pronounced background retinopathy (before hypophysectomy)*

Discussion

The present study of 68 patients with proliferative diabetic retinopathy showed that 49 retained a visual acuity of 0·33 in one or both eyes, and that at the last examination only eleven patients were blind. The decrease in vision was most pronounced in the group of nonhypophysectomized patients.

Deckert, Simonsen, and Poulsen (1967) also demonstrated that vision may be preserved for several years in diabetics with proliferative retinopathy, particularly in eyes with lesions in the retinal periphery. Kornerup (1958) reported that temporary visual improvement

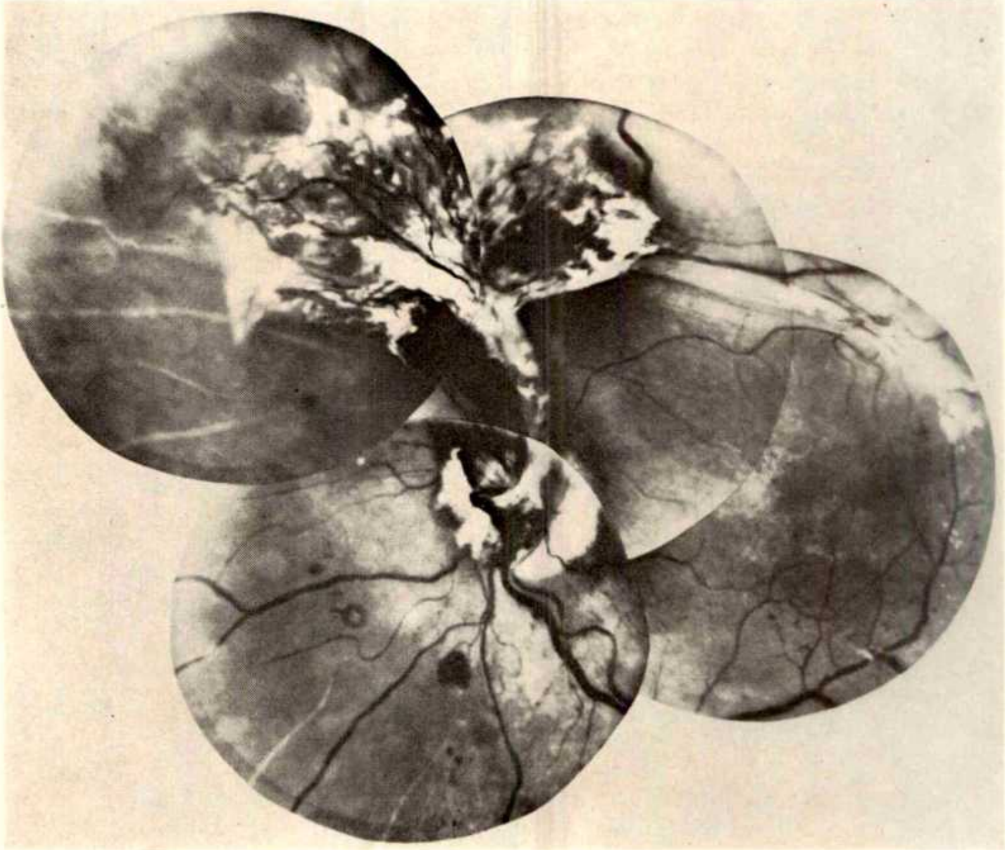

FIG. 11 *Same eye as in Fig.* 10, 31 *months later. Considerable progression in the proliferations; retinal detachment due to traction upwards temporally. Several arteries are transformed into white bands; otherwise the background retinopathy has improved*

occurred in five patients. Among 242 patients with proliferative diabetic retinopathy observed for 1 to 13 years, Beetham (1963) found that 82 retained a visual acuity of 6/12 or more, and 156 one of more than 6/60. He estimated that the average deterioration of the proliferative retinopathy from slight to extreme took approximately 5 years.

During recent years, reports have appeared on patients with arrest or even regression of the proliferations. Fischer (1961) mentioned four cases with regression in the retinopathy, and Dobree (1964) found that, in four eyes observed for 10 to 36 months, new-formed vessels on the retina had disappeared or considerably abated. Davis (1965) observed 55 patients for 6 to 36 months and found stationary conditions in fourteen eyes, and regression of new-formed vessels in four. Among 351 patients, Beetham (1963) observed spontaneous arrest in the proliferative retinopathy in 35, for more than 4 years in eight.

In the present series, proliferative retinopathy was stationary in 45 eyes. Proliferations did not develop in eight eyes during the observation period, and new-formed vessels disappeared in eleven eyes. Progression of the proliferative retinopathy was observed in nearly one half of the eyes in both hypophysectomized and nonhypophysectomized patients. Haemorrhages in the vitreous cavity with subsequent vascular and connective-tissue proliferations were seen with the same frequency in the two groups. It is remarkable, however, that in cases without haemorrhages in the vitreous cavity, gradual deterioration in the form of connective-tissue formation and neovascularization was far more frequent in the nonoperated group.

The visual prognosis is poor for eyes with proliferative diabetic retinopathy, but it appears that it is not as bad as is generally assumed. Hypophysectomy seems to postpone the aggravation of the fundus lesions, but strict clinical studies are required to prove or disprove this apparent tendency.

Summary

A series of 68 patients with proliferative diabetic retinopathy was observed for from 7 to 131 months. In 31 of the patients, hypophysectomy had been performed. Decrease in vision was observed in operated as well as nonoperated patients, but at the last examination only eleven patients were blind (visual acuity below 0·1 in both eyes).

Progression of the proliferative retinopathy was observed in 63 eyes; arrest in the development of the proliferations was seen in 45 eyes, and disappearance of new-formed vessels without concomitant formation of connective tissue in eleven eyes.

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Bilateral common carotid occlusion with hypoxic ocular sequelae

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A patient is described who was referred with anterior uveitis; following ophthalmic examination the diagnosis of carotid ischaemia was suspected. This diagnosis was confirmed by arch aortography which demonstrated bilateral common carotid occlusion with left vertebral artery stenosis. The aetiology of the occlusive process has been demonstrated at surgery. The patient's preoperative and postoperative progress has been evaluated by means of serial fluorescein angiography.

Case history

A self-employed milkman, aged 35 years, first presented at the medical outpatient department on August 10, 1969. He stated that 3 weeks previously he had suddenly lost the vision of the right eye. This lasted for approximately one hour and was followed by partial recovery. The eye had become inflamed and photophobic. In addition to his ocular symptoms he had also experienced several episodes of left hemiparaesthesia which lasted for a few minutes at a time. There was no associated weakness. He had also noticed that his jaws felt fatigued and ached when he was eating.

Family history His mother had died of a stroke.

General history He smoked twenty cigarettes a day and occasionally drank alcohol.

GENERAL EXAMINATION

He was a plethoric obese male. The blood pressure was 140/90 in the right arm, and 150/100 in the left; both radial pulses were present, but the carotid pulses were not palpable. Murmurs were noted over the right subclavian artery, over the abdominal aorta, and over both common iliac arteries. There was no other gross abnormality.

OCULAR EXAMINATION (August 14, 1969)

There was no lid swelling or proptosis on either side.

There was marked dilatation of the conjunctival vessels on the right; the cornea was clear and normal. Slit-lamp examination showed a dense flare in the anterior chamber without cells, keratic precipitates, or posterior synechiae. The pupil was dilated to 8 mm. with a markedly diminished response to both direct and consensual light stimulus. There was extensive new vessel formation in the iris which was atrophic and green-brown in colour in contrast to the left iris which was blue. The lens was clear but details of the fundus were blurred by vitreous haze. The disc showed some degree of pallor together with blurring of the margins. The retinal arteries were attenuated and irregular; there was marked venous beading with engorgement. Retinal oedema was most marked in the macular area. There were small scattered haemorrhages, microaneurysms, and areas of new vessel formation, mainly in the midperiphery, and there was a soft exudate temporal to the disc.

The left eye showed some vascular dilatation around the pupillary margin; fundus changes were

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similar to, but less severe than, those of the right eye (Figs 1 and 2). The eye was otherwise normal.

It was considered that these ocular changes were due to ischaemia from carotid obstruction.

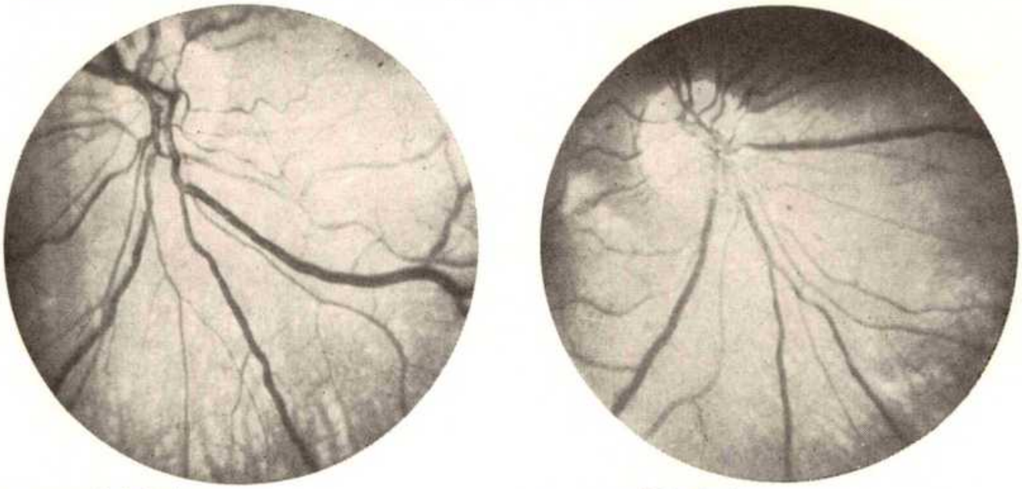


FIG. 1 *Left fundus* FIG. 2 *Right fundus*

INVESTIGATIONS

Hb 16·6 g.; White blood cells 9000/cu.mm.; Erythrocyte sedimentation rate 2 mm./1st hr

Serum cholesterol 346 mg./100 ml.

Blood urea 31 mg./100 ml. Serum electrolytes normal.

Total serum protein 6·9 g./100 ml. with an increase of α_2 and B globulins.

Wassermann reaction negative.

Nose and throat swab no pathogens isolated.

Arch aortogram (August 22, 1969) performed *via* the femoral artery. "The common carotid arteries were not demonstrated, both vertebral arteries appeared larger than normal. There seemed to be some stenosis at the origin of the left vertebral artery" (Fig. 3).

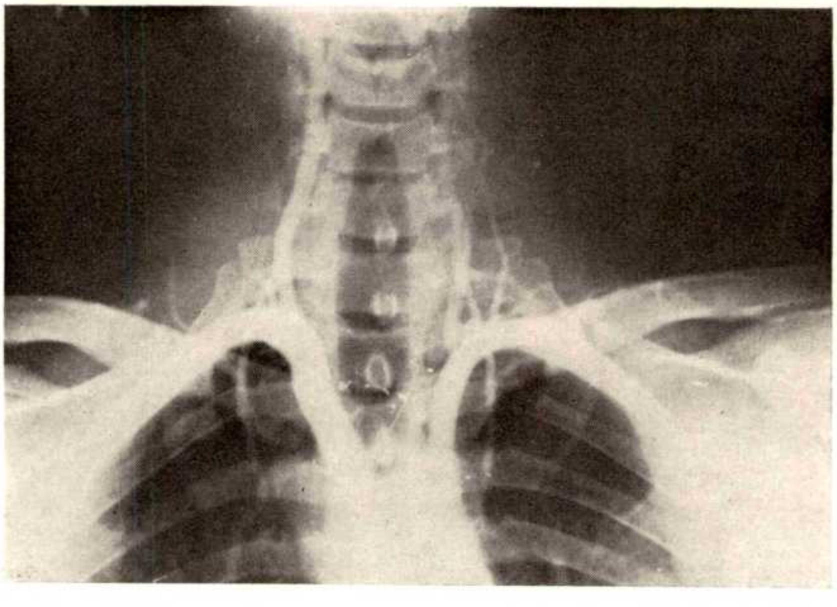


FIG. 3 *Preoperative arch aortogram*

OCULAR EXAMINATION (October 23, 1969)

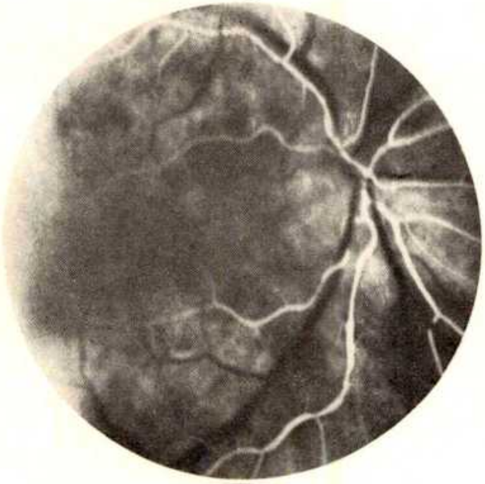
Increasing prominence of the left iris vasculature was noted, particularly of the circumpupillary arcade. Gonioscopy demonstrated peripheral anterior synechiae formation and new vessels involving the total angle circumference of the right eye; apart from a few visible radial vessels the left angle appeared to be normal. Applanation pressures were 14 mm. Hg in the right eye and 12 mm. Hg in the left. On neither eye was there any movement of the fluorescein meniscus which normally occurs with arterial pulsation. Peripheral fields were full to ¼° and 4° white targets.

FLUORESCEIN STUDIES

The fundi were observed and photographed after the injection into an antecubital vein of 3 ml. 25 per cent. sodium fluorescein. Events in the two eyes were similar both in appearance and timing. Arterial appearance of dye was noted at 15 sec. (Fig. 4); at 23 sec. there was only a minimal appearance of dye in the large veins forming a narrow stream along the vein walls. At 95 sec. streaming was still apparent and total venous filling failed to develop (Fig. 5). The picture of the left eye at 5 min. showed extensive leakage of dye from the venous side of the circulation (Fig. 6). The low visual acuity in the right eye can probably be accounted for by the filling defect of the right macular arterioles which supplied the areas of exudate temporal to the disc.

At this stage the patient was referred to St. Mary's Hospital.

(4)



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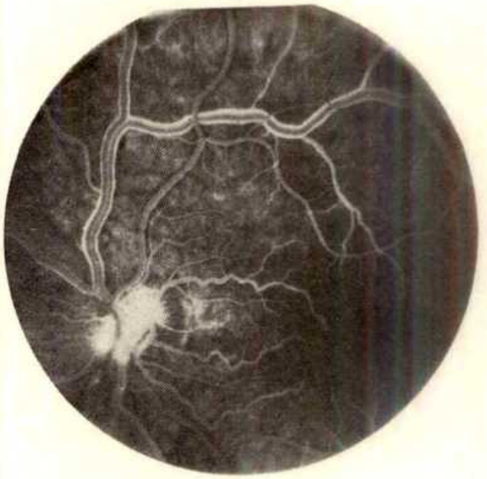
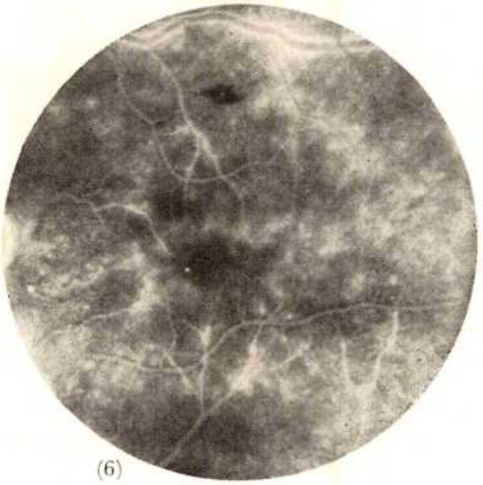




(6)

FIG. 4 15-*sec. right fluorescein angiogram; arterial phase, showing marked attenuation*

FIG. 5 95-*sec. left fluorescein angiogram, showing failure of total venous filling*

FIG. 6 5-*min. left fluorescein angiogram, showing venous leakage*

OPERATION (February 3, 1970 : Surgeon, Mr. H. H. G. Eastcott)

The left common carotid bifurcation was explored in the neck. The internal carotid and external carotid branches were both patent, but the common carotid artery was thrombosed. The bifurcation was opened and a Volmar stripper passed down the common carotid artery, and a large cone of atheroma was removed. This produced some flow. The left subclavian artery was then exposed above the clavicle and an 8-mm. by-pass Dacron graft was inserted from the third part of the subclavian artery to the left common carotid bifurcation, the graft being inserted inside in each instance. A good flow was restored in the left internal carotid artery.

PROGRESS

A postoperative arch aortogram showed that the graft appeared to have occluded postoperatively, although clinically it seemed patent.

OCULAR EXAMINATION (April 27, 1970)

The visual acuity in the right eye was 6/60 and in the left 6/9 with correction.

There was right bulbar conjunctival engorgement with corneal oedema but no evidence of stromal vascularization. The marked rubeosis of the right iris persisted and no pupillary response was elicited. Externally the left eye was normal. Perimetry showed some degree of contraction of the right field particularly to a ¼° white target. Applanation pressures were 42 mm. Hg in the right eye and 20 mm. Hg in the left. Detail of the right fundus was blurred by corneal oedema, but there was marked arterial attenuation with early optic atrophy. The left fundus showed arterial attenuation and venous distention with haemorrhages and arteriovenous anastomoses in the mid-periphery. He was treated with gutt. pilocarpine 2 per cent. three times a day to the right eye and Diamox Sustets 500 mg. daily by mouth.

FLUORESCEIN STUDIES

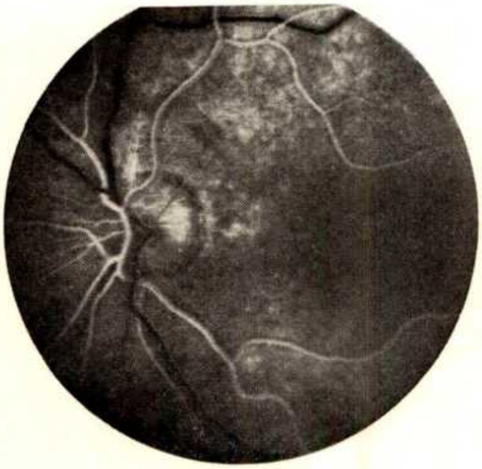
These were repeated in the left eye and showed an improved circulation. Early arterial filling occurred at 12 sec. and total venous filling at 22 sec. Arteriolar calibre was more regular and venous distention was reduced as compared with the preoperative pictures (Figs 7, 8, and 9, opposite).

Discussion

The symptoms and signs of the ocular pathology associated with severe stenosis or occlusion of the carotid circulation have been described by Skipper and Flint (1952) and amplified by numerous other authors, including Kearns and Hollenhorst (1963), Knox (1965), Crock (1967), and Sanders and Hoyt (1969).

The patient may present with symptoms of cerebral or ocular dysfunction separately or in combination. The ocular complaints characteristically consist of a transient loss of vision, often precipitated by changes in posture; pain in and around the eye without photophobia and a gradually progressive fall in visual acuity. On examination there may be lid swelling and dilatation of the conjunctival vessels; the cornea may show endothelial changes with folds in Descemet's membrane, oedema, and stromal vascularization. The iris is atrophic and shows increasing prominence of the vasculature; the pupil is commonly semidilated and sluggish in its responses, with ectropion of the iris pigment layer around the pupil margin. There is dense flare in the anterior chamber, sometimes with cells and keratic precipitates, but posterior adhesions between the iris and lens are not usual (Knox, 1965). The intraocular pressure is often normal or low initially, but a rise in tension may occur in association with new vessel and synechia formation in the anterior chamber angle (Smith, 1962). Cataract formation begins as a central opacity near the posterior pole of the lens and may progress rapidly to maturity. Examination

(7)



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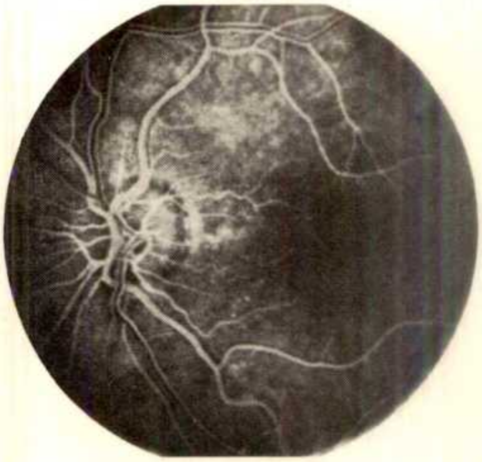

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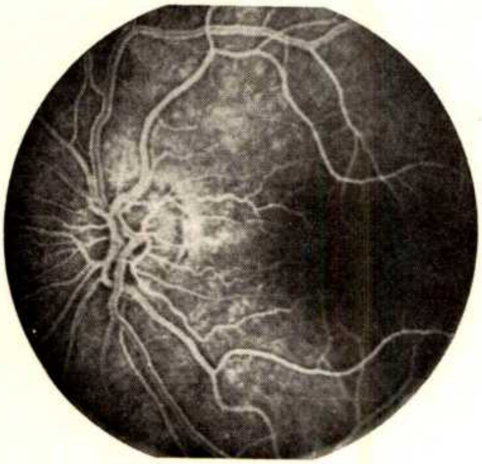

FIG. 7 12-*sec. left fluorescein angiogram, showing early arterial phase*

FIG. 8 18-*sec. postoperative left fluorescein angiogram, showing venous phase*

FIG. 9 22-*sec. postoperative left fluorescein angiogram, showing venous phase*

of the fundus may show pallor and oedema of the disc; the arteries are narrowed and irregular with venous engorgement and beading. The retina is oedematous, particularly in the macular area, and small scattered haemorrhages and microaneurysms occur mainly in the midperiphery together with small areas of fine new vessel formation (Kearns and Hollenhorst, 1963).

Similar changes take place in the anterior segment when surgery embarrasses the ciliary circulation, as may occur with muscle transplantation, detachment surgery, angiodiathermy, and more recently with cyclocryotherapy.

Graham (1968) states that a transient visual loss in one eye with often a contralateral motor or sensory defect is almost pathognomonic of internal carotid artery disease. He stresses the importance of angiographic confirmation. The arch aortogram of the patient we describe shows that his ocular circulation is supplied by his vertebrobasilar system, or *via* devious anastomotic channels since his entire carotid circulation on both sides is absent. Anciliary information concerning retinal circulation has been derived from serial fluorescein studies. David, Norton, Gass, and Sexton (1966) observed the retinal circulation in normal patients, in those undergoing carotid compression, and in those with proven carotid occlusion following the intravenous injection of fluorescein. They give normal figures of 10·9 sec. for arterial appearance time, 13 sec. for early venous fluorescence, and 17·6 sec. for total venous fluorescence. Our equivalent figures, using the same injection technique in this particular patient, are 15 sec., 23 sec., and not at all indicating delay in arterial appearance and gross delay in venous filling. David and others (1966) considered that "the best correlate of retinal circulatory insufficiency by this method is slow filling of the veins in the absence of venous obstruction". Hypoxic damage to vessel walls would be expected to be greatest on the venous side of the circulation as it is demonstrated in this patient by the fluorescein leakage (Fig. 7).

The patient's postoperative progress following arterial by-pass surgery has demonstrated an improvement in fluorescein appearance time and retinal vascular status, although the postoperative arch aortogram failed to show patency of the graft. Retinal venous distension and leakage have decreased and the iris vascular pattern has returned to normal in the left eye. Fluorescein studies may thus prove helpful in evaluating the results of arterial surgery.

Summary

A patient is described with proven atheromatous occlusion of both common carotid arteries and stenosis of the left vertebral artery, who developed transient neurological symptoms and severe bilateral hypoxic ocular pathology. His preoperative and postoperative progress has been evaluated by means of serial fluorescein studies of the retinal circulation.

We would like to thank Mr. A. Stanworth, Dr. A. W. D. Leishmann, and Mr. H. H. G. Eastcott, for their permission to publish this report of their patient. Our thanks are due also to the staff of the Photographic Department at the Royal Hospital, Sheffield, for their assistance with the illustrations.

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Iridocyclo-retraction in narrow-angle glaucoma

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No specific way has so far been found to treat the organic (synechial) closure of the anterior chamber angle. Iridectomy relieves the pupillary block but the iris root remains fixed to the filtering zone. Cyclodyalisis is as a rule useless, being followed by immediate re-adherence.

A new surgical procedure which has been developed is described in this paper as "iridocyclo-retraction". The iris root is forced by two (or more) interposing autoimplants of scleral tissue (Fig. 1).

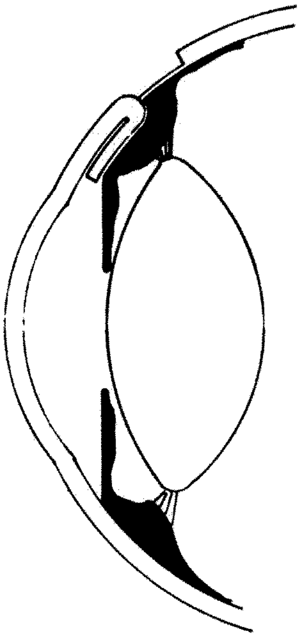

FIG. 1 *General principle of iridocyclo-retraction*

So-called "setons" of various substances (plastics, etc.) have already been tried to keep the cyclodialysis cleft open. The new procedure has two important features:

(*i*) It aims to restore the normal access of the aqueous to the outflow pathways (rather than to provide a new connection between the anterior chamber and the suprachoroidal space, as in cyclodialysis).

(*ii*) It is autoplastic.

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Preliminary studies

Experiments on rabbits (Lakomkin, 1970) have shown that the procedure is well tolerated by the eye, and that it achieves its object of restoring access to the normal outflow system.

Histological studies showed that additional outflow routes might be formed along the autoimplants, and endothelium-lined slits have, in fact, been found to form. Connection with the suprachoroidal space may occasionally result, but this is not the main purpose of the procedure.

An exceptionally interesting case was observed by Shmeleva (1970); a patient who had undergone iridocyclo-retraction died a month later from an unrelated cause. It was found at the *post mortem* examination that the angle was open, whereas before the operation it was nearly closed.

Surgical technique (Fig. 2, opposite).

Local anaesthesia is achieved by a retrobulbar injection of 2 ml. procaine 2 per cent. solution; another 2 ml. of the same solution is injected along the superior rectus muscle and (on withdrawal of the needle) under the conjunctiva.

An incision is made in the conjunctiva 8 mm. from the limbus, usually between 11 and 1 o'clock, and the sclera is exposed almost to the limbus. The rectus muscle is clamped by a small haemostat to diminish the blood supply to the operated region.

Two small (2 × 4 mm.) pedicles are then outlined by nonperforating incisions of the sclera (Fig. 2), 4–8 mm. from the limbus. The two areas should be about 5 mm. apart; the width of the muscle insertion is a convenient criterion.

Next the sclera is laminated inside the outlined zones, leaving approximately one-third of its thickness below. Anteriorly (4 mm. from the limbus) the two pedicles remain attached to the sclera.

Cuts are then made at the base of the flaps through the remaining layers into the suprachoroidal space, and bleeding points are cauterized.

A thin cyclodialysis spatula is introduced beneath the sclera into the anterior chamber angle. The roots of the iris and the anterior part of the ciliary body are gently separated from the sclera between the two flaps. A strong pressure on the eye is exerted for about 1 min. to prevent bleeding into the anterior chamber.

The most delicate (and very important) step is the introduction of the scleral pedicles into the anterior chamber angle; for this the following technique can be recommended:

A thin round needle (as used in vascular surgery) is grasped by the needleholder, and the anterior half of the needle (5 mm.) is straightened out. The free end of the pedicle is picked up by the needle point and then pulled forward under the sclera. The attachment of the pedicles to the sclera prevents them from being pushed too far in the anterior chamber (their ends should be at the limbus). Their position can easily be corrected by a thin spatula. When the needle is withdrawn it slips off leaving the flaps in place.

We have also tried "free" autoimplants (using scleral tissue or auricular cartilage), but their placing is more difficult.

Air is injected into the anterior chamber, care being taken not to cover the pupillary region by the bubble (which may cause an air block). The conjunctival incision is closed by an uninterrupted suture.

COMPLICATIONS

The procedure is essentially simple, but requires attention given to minute details. The same complications may arise as in cyclodialysis: iridodialysis, perforation of the ciliary body, detachment of Descemet's membrane, etc. They result from technical errors and need not be discussed here.

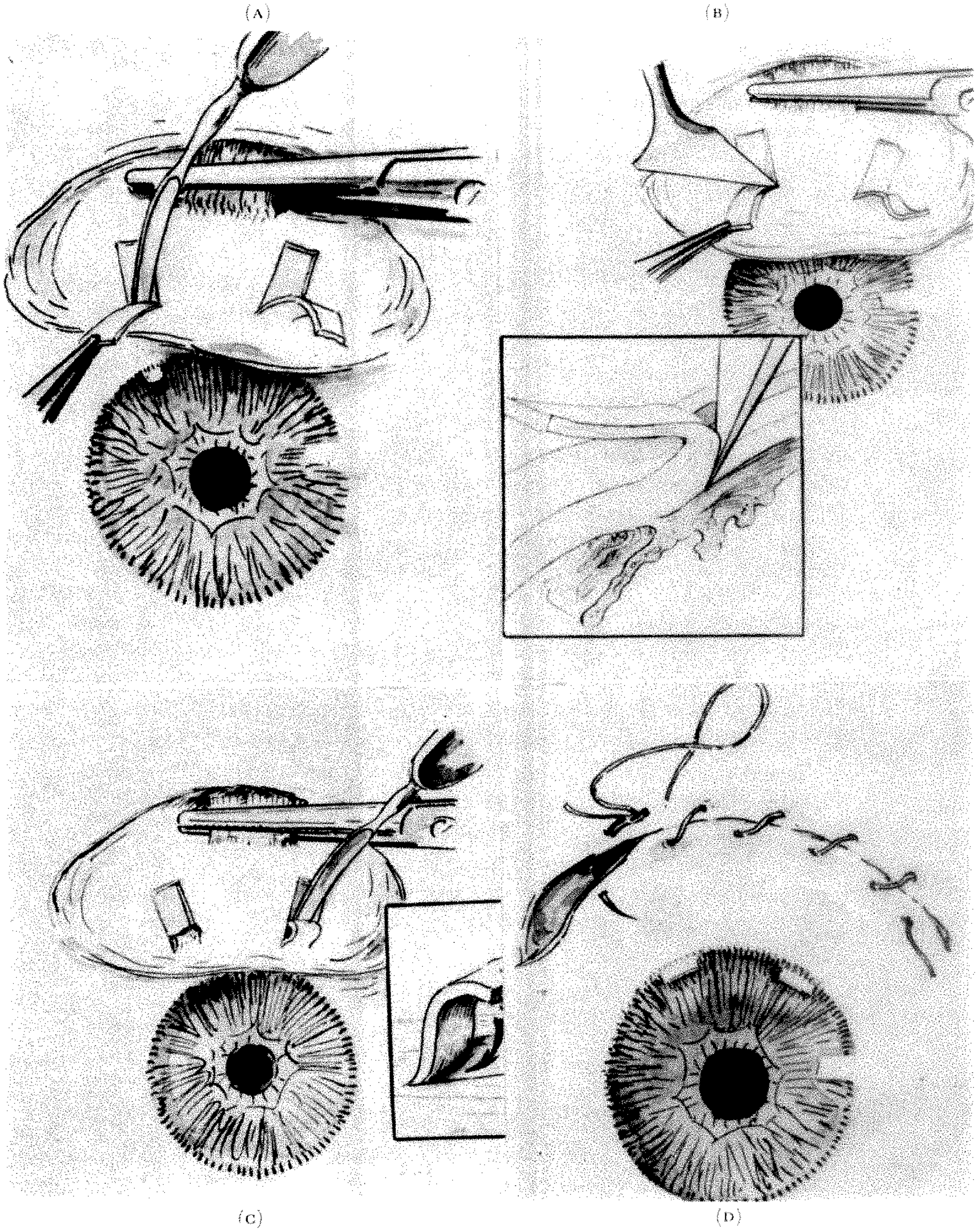


FIG. 2 *Technique of iridocyclo-retraction (a,b,c,d). For explanation see text*

The greatest care should be taken to avoid bleeding into the anterior chamber, which predisposes to synechia formation and may nullify the effect of the operation.

The critical moment is that of separation of the iris root from the ciliary body. A sufficiently strong pressure (for instance, by a cotton swab) on the eye is a routine and effective preventive measure. In the process of separation the 3 and 9 o'clock meridians are to be avoided (because of the large vessels in the vicinity).

If, in spite of all precautions, blood appears in the anterior chamber, air should be quickly injected. This raises the intracoular pressure and forces the blood out, at least from the pupillary region.

Occasionally the anterior chamber can be irrigated (using urokinase or a similar solution).

To minimize the risk of postoperative haemorrhage, rest in bed for 3 days is advisable.

In cases of severe and slowly-absorbing hyphaema, the latter should be washed out on approximately the 10th day (by way of a paracentesis).

POSTOPERATIVE COURSE

Inflammation is usually mild, but a tendency to posterior synechia formation may occasionally be observed up to the 6th or 8th week postoperatively. The pupil should be kept dilated to about 5 or 6 mm.

A stronger mydriasis is indicated only when necessary for periodical examination, prevention, or rupturing of the synechiae, etc.

Steroids are used locally three or four times a day starting from the day of operation. When inflammation has subsided, so long as there is no sign of corticosteroid hypertension, the daily instillation may sometimes be continued for as long as 2 or 3 months.

Anticholinesterase miotics are contraindicated both before and after the operation.

Indications for use

The procedure is aimed solely at eliminating the iris-block of the angle. A narrow angle is easily identified by gonioscopy. The Forbes corneocompression test (Forbes, 1966) proved helpful in estimating the extent of synechia formation and in differentiating between functional and organic blocks. Changes in the angle profile after the administration of strong osmotic agents (urea, glycerol) also assist diagnosis.

In acute glaucoma it is often difficult to differentiate the functional from the organic changes. Iridectomy is therefore the method of choice, and if necessary iridocyclo-retraction may be performed as a second-step procedure

The operation seems to be of great value in cases of aphakic glaucoma. Its combination with cataract extraction has also proved very promising and is being tried on a wide scale. It has also been successfully used in cases of secondary glaucoma with synechial angle closure.

Re-operation

Iridocyclo-retraction aims at restoring the free access of the aqueous to the outflow channels. But these outflow passages themselves may be damaged; in particular the trabecular meshwork may suffer from long-standing iris adherence. It is therefore important to ascertain whether a "surgical success" (*i.e.* opening of the angle) has been achieved.

If the angle has been opened, a completely different type of intervention is needed on the intramural outflow passages. This may be trabeculectomy (after Cairns), trabeculotomy, or other methods. This second-stage procedure has to be carried out over the area of the opened angle (*i.e.* between the implants). On the other hand, if the angle still remains closed, the object of the subsequent procedure is the same as that of the first.

Re-adherence of the iris root between the implants may sometimes follow if they have been placed too far apart; the space between them should not exceed 5 mm., and if this happens iridocyclo-retraction should be repeated.

Separation of the iris root is carried out in the same region and a third pedicle is introduced between the former two (Fig. 3, opposite).

(3)

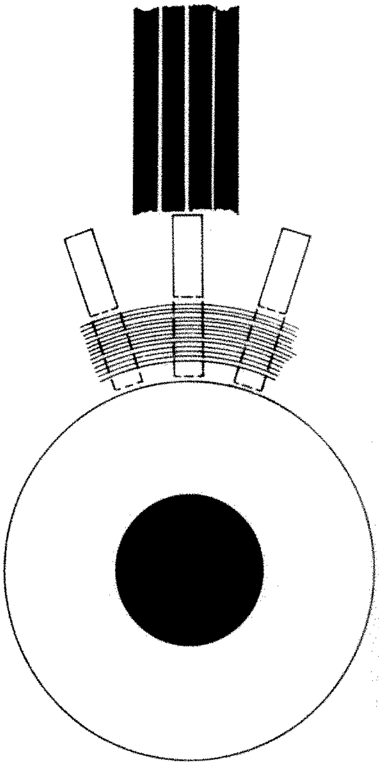
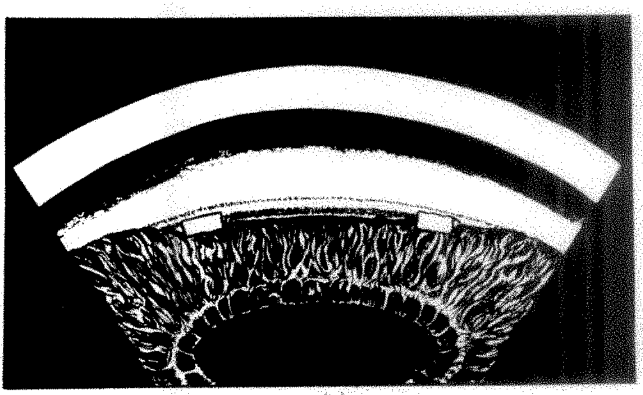


FIG. 3 *"Three-point" version of iridocyclo-retraction. The black bars indicate the position of a rectus muscle (usually the superior). The area of opening of the anterior chamber angle is plotted by the concentric lines*

FIG. 4 *Diagram illustrating gonioscopic view after iridocyclo-retraction. The angle is opened between the autoimplants*



(4)

Sometimes, when it appears that the thrust behind the iris is too strong, this "three-point" iridocyclo-retraction is done as a primary procedure.

Results

141 iridocyclo-retraction operations have so far been performed (including 23 in cases of aphakia). It is now commonly used in everyday practice and the maximum follow-up is 3 years. The anterior chamber angle was successfully opened after the first procedure in 128 of 141 eyes, and a second "three-point" iridocyclo-retraction resulted in opening the angle in seven of the remaining thirteen cases.

Ocular hypertension recurred in 22 cases after the angle had been opened, and a second operation (trabeculectomy, sinusotrabeculotomy) was followed by reduction of the ocular tension to normal in fifteen of these cases.

The tension was controlled after the first procedure in about 80 per cent. of cases, and the second operation brought the success rate to about 90 per cent. A longer follow-up is needed to confirm these data.

In one case a choroidal detachment developed after the operation, but this disappeared spontaneously in a few days.

A long-standing hypotony observed in four cases seemed to hasten pre-existing cataractous changes.

The gonioscopic picture after an iridocyclo-retraction operation is very characteristic (Fig. 4). The autoimplants are clearly seen to protrude into the anterior chamber angle from behind. When the procedure has been successful, the angle is opened between the pedicles.

Discussion

It will be remembered that this iridocyclo-retraction operation forms part of a system of nonfistulizing glaucoma surgery (Krasnov, 1968, 1969). This has been described elsewhere and is summarized in the Table.

Table *Nonfistulizing glaucoma surgery*

Causes of intraocular hypertension		*Surgery*
Iris-block (angular) retention	(*a*) Functional	Iridectomy
	(*b*) Organic (synechial)	Iridocyclo-retraction
Pretrabecular obstruction by foreign tissue		Goniotomy
"Trabecular" retention		Trabeculotomy or trabeculectomy
"Intrascleral" retention		Sinusotomy
"Hypersecretion" glaucoma		Cycloanaemization
Combination of causes		Combined procedures

If used alone, iridocyclo-retraction is indicated for iris-block (narrow-angle) glaucoma only. If iris-block is combined with intramural (usually, trabecular) damage, iridocyclo-retraction can be combined with the appropriate procedure in the above system.

The operation is not recommended for wide-angle glaucoma, because a hypertensive effect may ensue owing to drainage into the suprachoroidal space (as in cyclodialysis).

Although iridocyclo-retraction is primarily aimed at synechial angle closure, it is also quite efficient in cases of functional iris-block. The choice between iridectomy and iridocyclo-retraction is therefore of clinical importance. Iridectomy has traditionally been the method of choice. It is simple and safe, but it is usually insufficient in the presence of the extensive goniosynechiae which commonly occur in narrow-angle glaucoma. In short, iridectomy is promising only in certain cases of glaucoma due to anomalies of the angle, whereas iridocyclo-retraction is nearly always so.

The mechanics of the hypertensive action of iridocyclo-retraction deserve some consideration. Several factors may be involved: opening of the angle, drainage into the suprachoroidal space, new-formed outflow channels along the autoimplants, and the inhibition of aqueous production by the ciliary body.

The paramount question is whether the effect is due to an increase in outflow or to a decrease in aqueous formation.

Repeated tonographic investigations (Lakomkin, 1970) over a 12-month period after sixteen uneventful iridocyclo-retractions showed the following data:

Before surgery:
Average $C = 0{\cdot}10 \pm 0{\cdot}01$; $F = 1{\cdot}2 \pm 0{\cdot}18$; P_0/C 342 ± 76

After surgery:
Average $C = 0{\cdot}24 \pm 0{\cdot}01$; $F = 0{\cdot}9 \pm 0{\cdot}12$; P_0/C 55 ± 4

This suggests than an improvement in the outflow facility is the principle factor, though some reduction in aqueous formation may also result.

The conventional procedures are not always satisfactory in cases of synechial angle closure. Even the traditional fistulizing surgery is here less effective. Iridencleisis though widely used, is actually one of the most injurious procedures in glaucoma surgery, and I have practically abandoned its use.

Summary

A new surgical prodecure (iridocyclo-retraction) has been developed for narrow-angle glaucoma, especially in cases with synechial iris closure. The iris root is forced back from the filtering zone and kept back by two (sometimes three) interposing autoimplants of scleral tissue. The operation has been successfully tried in 141 cases during a 3-year period. Experiments on rabbits have shown the method to be based on sound principles. Iridocyclo-retraction has substantial advantages over iridectomy and iridencleisis and deserves a wider clinical use.

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Colobomatous cupping of the optic disc

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Coloboma confined to the optic disc is a relatively rare condition (Steinberg, 1943), and has been described as unilateral in the majority of cases (Duke-Elder, 1964; François, 1964). However, manifestation of the deformity may occur in the other eye (Hughes, 1947), and a number of bilateral cases have now been described. This paper records another bilateral case.

Case report

A 35-year-old man was found to have defective vision in the right eye at a routine medical examination and was referred for ophthalmic examination. He gave a history of poor vision in the right eye since childhood, and of having first been seen by a doctor at the age of 23 when living in India. He was told that he had a "lazy eye" for which no treatment could be given. There was no previous history of ocular trauma and no relevant medical history. A family history was not available.

GENERAL PHYSICAL EXAMINATION

The patient was a fit young man of distinctly asthenic physique with arachnodactyly and low-set ears.

VISUAL ACUITY

Right eye 6/36 and N14, not improved (−1·75 D sph.)

Left eye 6/9 and N5, not improved (−0·25 D sph.).

ANTERIOR SEGMENT

Posterior embryotoxon was present, most marked on the temporal aspect of both eyes, and the anterior chambers were of moderate depth. No abnormality was detected in either iris or lens and the vitreous was clear. The applanation tension was 18 mm. Hg in each eye. The angles were open with a well-marked line of Schwalbe, corresponding to the embryotoxon, and numerous pectinate fibres.

FUNDUS

The right disc (Fig. 1) was greater than average size with a small inferior conus and was deeply cupped, the lower half being glistening white. The upper half was of good colour with a sharp overhang which concealed the vessels at the disc margin.

The left disc (Fig. 2) was slightly greater than average size and deeply cupped over most of its area. The vessels emerged at the base of the cup through a nasally directed scleral canal, the temporal branches following the rim of the cup to make a steep exit from the temporal aspect. The nasal branches made a more direct exit by surmounting the overhanging edge of the cup on the nasal side.

No other fundus abnormality was found.

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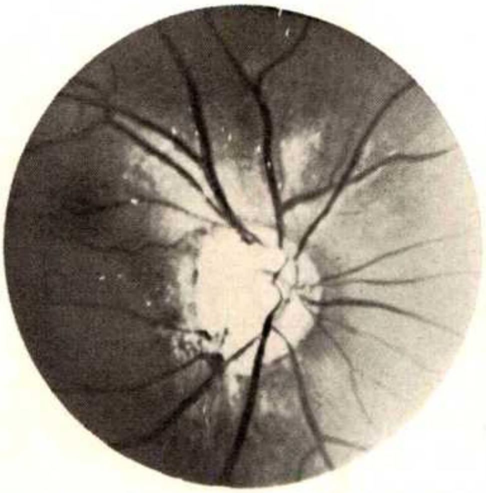

FIG. 1 *Colobomatous cupping of right optic disc*

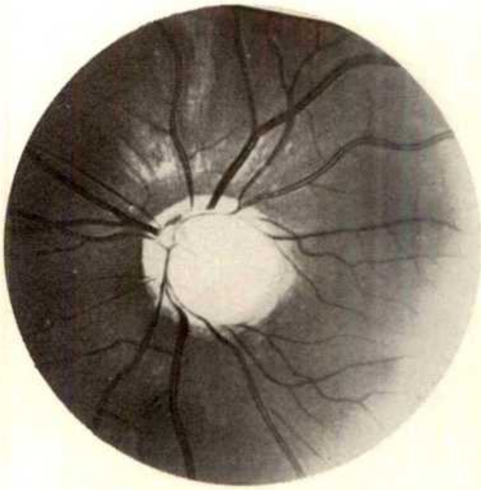

FIG. 2 *Colobomatous cupping of left optic disc*

VISUAL FIELDS

A dense nerve fibre bundle type of defect affected most of the upper half of the right visual field (Fig. 3) and an arcuate scotoma was delineated below the fixation point in the left (Fig. 4).

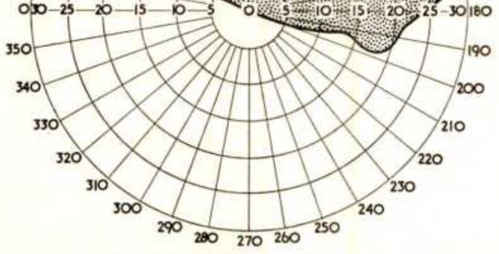

FIG. 3 *Visual field defect. Target 2/1000 white. Visual acuity 6/36*

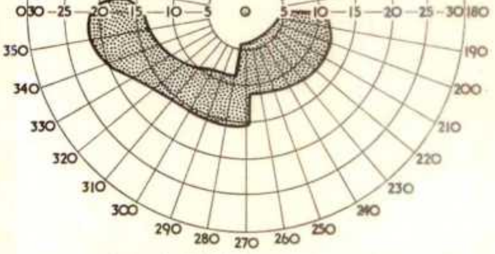

FIG. 4 *Visual field defect. Target 2/1000 white. Visual acuity 6/9*

PROGRESS

The patient has been observed at intervals of 3 months over a period of 2 years, during which time the applanation tension has never been greater than 18 mm. Hg in each eye and serial static perimetry has shown no change in the field defects.

A water drinking test produced a rise of 6 mm. Hg in each eye after 1 hour with a return to the baseline after 90 min.

DIAGNOSIS

Colobomatous cupping of the optic disc.

Discussion

Bilateral typical coloboma confined to the optic disc is a developmental abnormality, the chief importance of which lies in its differentiation from progressive ocular diseases requiring early recognition and treatment. Such diseases include glaucoma (von Szily, 1901; Hillion, 1911; Steinberg, 1943; Hughes, 1947; Gaipa, 1960), bilateral optic atrophy (Adler, 1937), and bitemporal field defects (Rucker, 1946). Strictly defined as above, this abnormality is an exceedingly rare condition (Hillion, 1911). The literature provided details of 24 cases of which only eleven were bilateral.

The condition has been described under various names, coloboma of the optic nerve head (Terrien and Petit, 1901), coloboma of the optic disc (Hird, 1912), colobomatous cupping of the optic disc (Del Rio Cabanas, 1949), low-grade coloboma of the optic disc (Henkind, 1963), and partial coloboma of the optic nerve (François, 1964).

The clear-cut clinical picture is almost identical in every case, with unequal visual loss (Steinberg, 1943; Hughes, 1947), nerve fibre bundle defect (Steinberg, 1943; Rucker, 1946; Magnus, 1946; François, 1964; Riise, 1966; Kim and Hung, 1967), the typical appearance of the optic disc, and the arrangement of the vessels adequately described by Caspar (1887). There is usually no other abnormality in the fundus.

AETIOLOGY

This condition has been well documented clinically (Steinberg, 1943; Del Rio Cabañas, 1949; Offret, 1967) and experimentally (Nicholls and Tansley, 1938; Payne, 1941). The inferior situation of cup in all cases described suggests the distal extremity of the embryonic fissure as the likely site of the abnormality. Closure of the embryonic fissure begins at the 11 mm. stage and is normally complete by the 15 mm. stage (Offret, 1967). Some controversy exists over which germinal layer is initially at fault, ectoderm (Offret, 1967) or mesoderm (Calhoun, 1930). However, most authorities are agreed that the origin of the defect lies in excessive proliferation of the inner layer of the optic cup. This is simply an exaggeration of the normal mechanism of closure. Since the first sign of orientation of the paraxial mesoderm does not appear until the 18 mm. stage (Pedler, 1961), abnormal ingrowth of mesoderm can play only a sequential role in causation (Steinberg, 1943). The inheritance of typical coloboma as an irregular dominant with varying expressivity and greater than 30 per cent. penetrance is well established (Duke-Elder, 1964).

ASSOCIATED DEFECTS

Arachnodactyly (Curtius, 1959), low-slung ears (Manara, 1959), and mandibular dysostosis (François and Haustrate, 1954) have been described in association with typical coloboma. No previous mention of posterior embryotoxon has been found in association with colobomatous cupping, although Kim and Hung (1967) described "limbal leucomas". The presence of a myopic error of refraction has been reported in most of the cases on record (Terrien and Petit, 1901; Hillion, 1911; Rucker, 1946; Hughes, 1947; Caccamise, 1954; Kruse and Utermann, 1963; Ernyei, 1964; François, 1964; Kipiotis and Theodosiadis, 1964; Riise, 1966).

DIFFERENTIAL DIAGNOSIS

Hypoplasia of the optic nerve can always be distinguished by the small size of the optic disc and is often accompanied by radiological evidence of a small optic canal on the same side (Ewald, 1967).

The myopic crescent is commonly temporal and progressive, and may be accompanied by other signs in the fundus (Caccamise, 1954; François, 1964).

Differentiation of colobomatous cupping from glaucomatous cupping may present problems, especially when accompanied by nerve fibre bundle defects (Hillion, 1911; Magnus, 1946; Hughes, 1947). Amblyopia is always present from an early age and the typical colobomatous cup is deepest in the lower half of the disc, resulting in a corresponding field defect which is non-progressive. Provocative tests to detect the presence of embarrassed outflow are negative (Magnus, 1946). The presence of coloboma results in the unusual arrangement of vessels on the disc, already noted.

Adler (1937) and Rucker (1946) have reported cases initially diagnosed as pituitary tumour, and Caccamise (1954) drew attention to the presence of a bitemporal field defect in his case.

Summary

A case of bilateral colobomatous cupping of the optic disc, with field defect, and associated abnormality is presented. Attention is drawn to the importance of differentiating this condition from progressive ocular disease requiring treatment.

I thank Surgeon Captain T. C. Barras, Royal Navy, for his help in the preparation of this paper.

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Fluorescein iridography

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The behaviour of anterior segment inflammation, as regards its temporal aspects, can be objectively assessed thermometrically (Mapstone, 1968); conclusions of spatial distribution can, only be inferred. If the extent of inflammation could be demonstrated, a correlation of temporal pattern with spatial distribution would allow a more precise interpretation of the clinical characteristics of anterior uveitis with attendant diagnostic, prognostic, and therapeutic gain. The purpose of this paper is to describe a method of investigating the spatial distribution of anterior uveitis, and the intensity of its vascular component, based on the reaction of normal and pathological iris vessels to injected fluorescein.

Material and methods

A Zeiss fundus camera and flash unit with an Ilford bright spectrum blue No. 622 gelatine filter for excitation and a Kodak Wratten 15 yellow filter as barrier was used for angiography. Photographs were taken prior to intravenous injection of 3 ml. 25 per cent. fluorescein, and 10 sec. later, at 2 sec. intervals for 40 sec. Final photographs were taken 5 min. after injection.

The material consisted of 48 normal subjects, 44 patients with vein occlusions, 68 patients with anterior uveitis, and seventeen with miscellaneous ocular conditions.

Results

NORMAL ANGIOGRAM

(*A*) *Preinjection fluorescence*

Control photographs taken before injection show either no image or a vague outline of lids and periocular tissue. The lens, however, shows a variable fluorescence which is most marked in the elderly (Fig. 1, opposite).

(*B*) *Postinjection fluorescence*

The sequence of photographs in Fig. 2 shows the anterior segment response to injected fluorescein, *viz.* pupillary fluorescence due to retinal vessel filling followed by a gradual leak into conjunctiva and skin. Pupillary fluorescence is dependent upon a relatively dilated pupil and lessens or disappears after the first dye transit. The normal iris exhibits one of the following patterns:

(1) No fluorescence, more common in younger patients whose stromal tissue has not yet atrophied. It is not dependent on degree of pigmentation since even blue irides may not fluoresce.

(2) Transient fluorescence during the first dye transit (Fig. 3, overleaf).

(3) Vessel fluorescence during the first dye transit, which then regresses and is followed by a perceptible blush of vessels and iris stroma (Fig. 4, overleaf).

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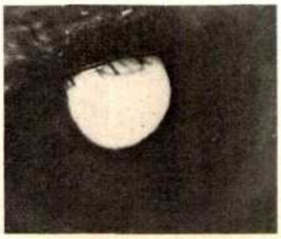


FIG. 1 *Fluorescence of ageing lens, pre-injection photograph*

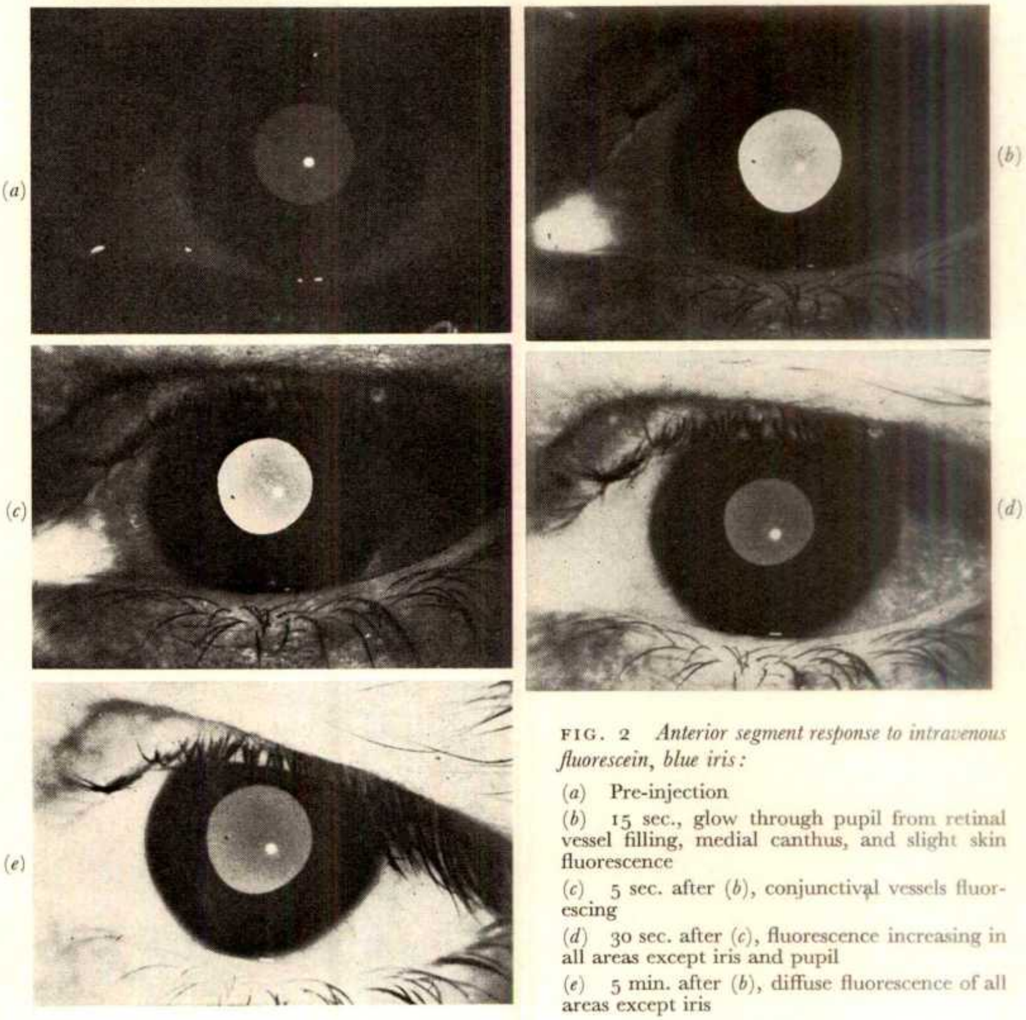


FIG. 2 *Anterior segment response to intravenous fluorescein, blue iris:*

(*a*) Pre-injection

(*b*) 15 sec., glow through pupil from retinal vessel filling, medial canthus, and slight skin fluorescence

(*c*) 5 sec. after (*b*), conjunctival vessels fluorescing

(*d*) 30 sec. after (*c*), fluorescence increasing in all areas except iris and pupil

(*e*) 5 min. after (*b*), diffuse fluorescence of all areas except iris

Normal iris fluorescence shows the following characteristics:

(a) The first part of the anterior segment to fluoresce is the caruncle; a time lag of up to 8 sec. elapses before iris vessels fluoresce.

(b) The number of vessels fluorescing increases with time.

(c) Not all vessels (or what appear to be vessels) fluoresce.

(d) Leakage into the iris stroma (as distinct from vessel wall) is minimal, and does not occur during the first dye transit.

(e) Little aqueous fluorescence is seen in photographs.

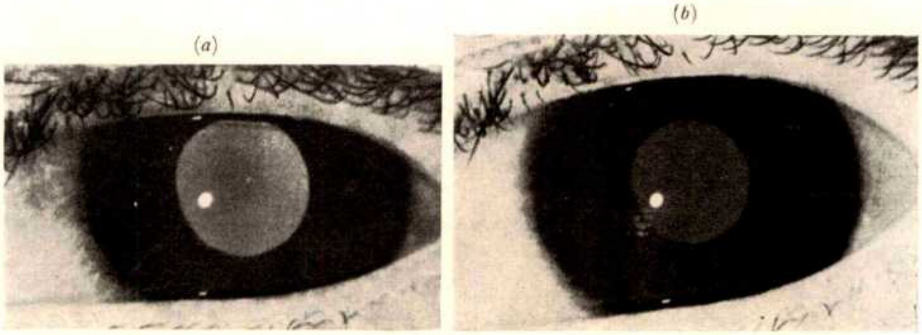
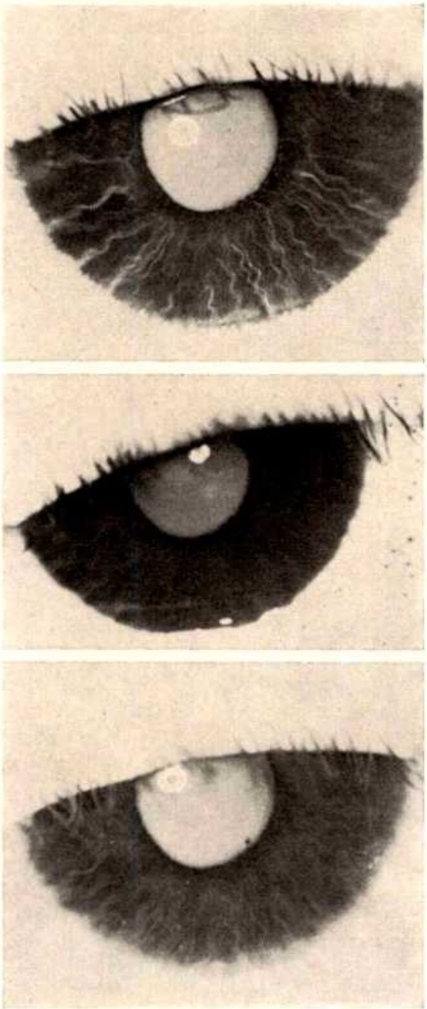


FIG. 3 *Fluorescence during first dye transit, blue iris:*

(*a*) 20 sec. after injection, vague fluorescence of iris vessels

(*b*) 40 sec. after (*a*), no iris fluorescence



(*a*) 20 sec. after injection, maximal fluorescence of iris vessels

(*b*) 60 sec. after (*a*), some fluorescence of iris vessel wall

(*c*) 5 min. after (*a*), light, diffuse fluorescence of vessels and stroma, excluding area between pupil margin and collarette, *i.e.* true tissue fluorescence not due to aqueous haze

FIG. 4 *Biphasic response of normal blue iris*

ABNORMAL ANGIOGRAM

(*A*) *Lightly pigmented irides*

Inflamed and new vessels both fluoresce; Fig. 5 shows a sequence from a patient with neovascularization secondary to proliferative diabetic retinopathy.

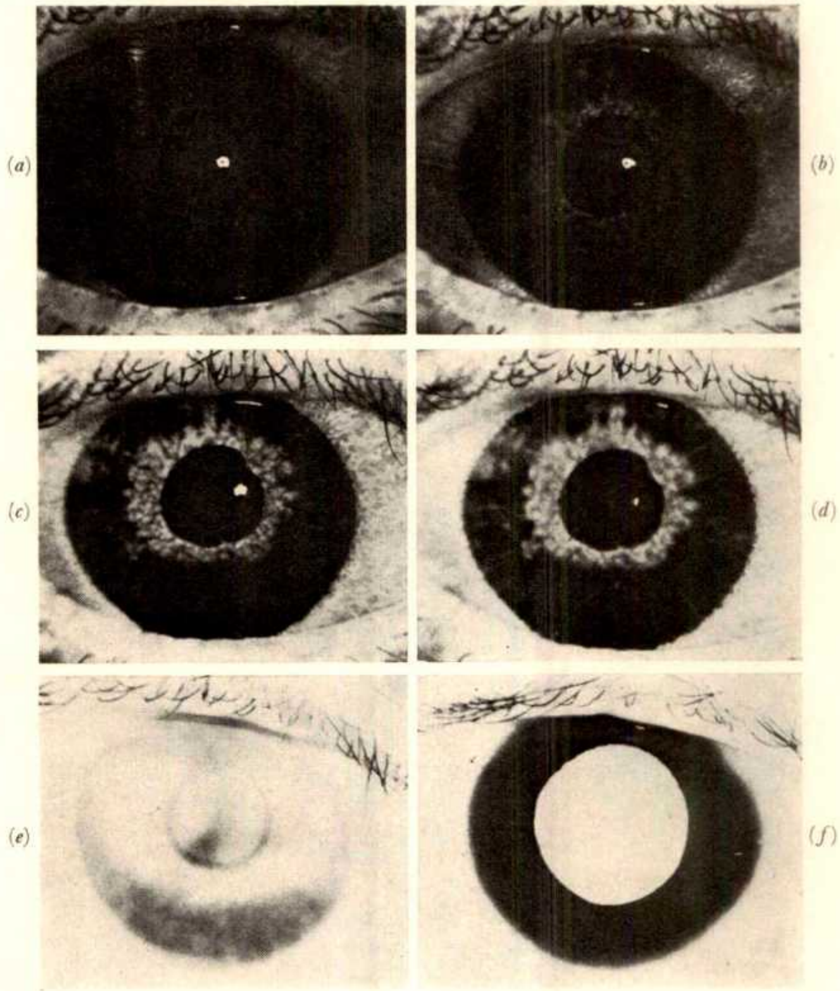


FIG. 5 *Fluorescence secondary to neovascularization* (*proliferative diabetic retinopathy*)

(*a*) 17 sec. after injection, light fluorescence of conjunctiva and periorbital skin
(*b*) 2 sec. after (*a*), new vessels leaking into stroma before normal iris vessels fluoresce
(*c*) 6 sec. after (*b*)
(*d*) 8 sec. after (*b*) diffuse peripupillary blush with blush of normal iris vessel walls
(*e*) 5 min. after injection
(*f*) 5 min. after injection, contralateral eye, no iris blush. Note intense pupillary fluorescence from retinal new vessels

Fig. 6 (overleaf) shows a sequence from a patient with diffuse iridocyclitis. It has the following characteristics:

(a) A variable time lag between conjunctival and iris fluorescence.

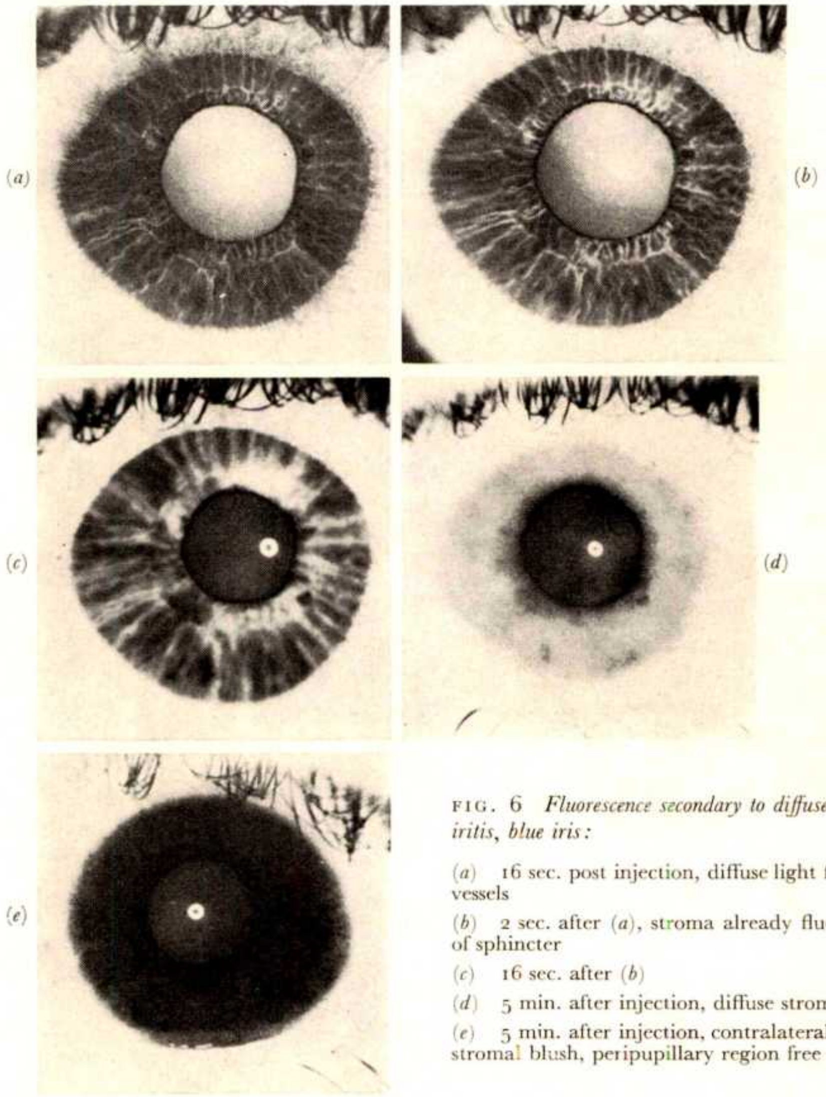


FIG. 6 *Fluorescence secondary to diffuse nongranulomatous iritis, blue iris:*

(*a*) 16 sec. post injection, diffuse light fluorescence of iris vessels

(*b*) 2 sec. after (*a*), stroma already fluorescing in region of sphincter

(*c*) 16 sec. after (*b*)

(*d*) 5 min. after injection, diffuse stromal haze

(*e*) 5 min. after injection, contralateral eye, diffuse, light stromal blush, peripupillary region free

(b) All abnormal vessels fluorescing do so practically simultaneously.

(c) The spatial distribution of fluorescence depends on that of the inflammation, but even in a diffuse reaction not all (putative) vessels fluoresce. In early rubeosis the spatial distribution varies with the extent of neovascularization; in late rubeosis both normal and new vessels leak.

(d) Fluorescence increases with time.

(e) Diffusion into surrounding stroma occurs during the first dye transit, followed by diffuse aqueous fluorescence.

(*B*) *Heavily pigmented irides*

(1) Negroid and mongoloid

Little of value can be obtained from these angiograms, there being either a fluorescein leak from the pupil margin or a diffuse aqueous haze.

(**2**) Caucasoid

Pigmentation is usually not of uniform density and through its interstices fluorescence can be seen. From the distribution and time sequence conclusions can be drawn based on the more obvious behaviour of lightly pigmented irides (Fig. 7).

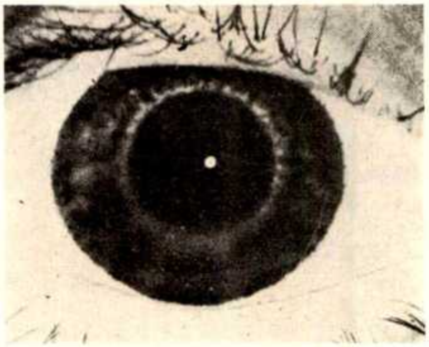


FIG. 7 *Fluorescence secondary to diffuse nongranulomatous iridocyclitis, Caucasian, brown iris. Photograph 24 sec. after injection,* i.e. *fluorescence can only have come from inflamed vessels*

Discussion

Normal anterior uvea leaks fluorescein in sufficient quantities to be measured by a fluorometer (Amsler and Huber, 1946; Langham and Wybar, 1954). Photographically two distinct types of fluorescence have to be distinguished, *viz.* intravascular due to the first dye transit and extravascular dependent upon a leak of fluorescein into the vessel wall and stroma.

The photographic detection of intravascular fluorescence is determined—amongst other things—by:

(**1**) A patent vessel

(**2**) Thickness and pigmentation of vessel wall

(**3**) Pigmentation of anterior border layer of iris

(**4**) Concentration of fluorescein

The temporal characteristics of this type of fluorescence are illustrated in Fig. 8, *i.e.* fluorescence during the first dye transit only (see Fig. 3).

Any further fluorescence in an iris angiogram must be extravascular, within the vessel wall, iris stroma, or aqueous. Its photographic detection will depend on the abovementioned factors and in addition upon vessel wall and endothelial permeability, the latter being the limiting factor. Its temporal characteristics are illustrated in Fig. 9, the gradient of the graph depending largely on endothelial permeability.

There may, however, be a combination of both intra- and extravascular fluorescence and if endothelial permeability is increased, as in an inflamed vessel, the intravascular component will be "swamped" by a rapid fluorescein leak (Fig. 5) and the pattern of Fig. 9 will be produced. Again, in some patients, if endothelial permeability is not pathologically increased, the pattern of fluorescence shown in Fig. 10 is produced, *i.e.* fluorescence during the first dye transit followed by a gradual extravascular fluorescence (Fig. 4).

The essential difference, therefore, between a normal and abnormal iris vessel is the leak of fluorescein from the latter during the first dye transit, allowing a ready demonstration of the spatial distribution of anterior uveal pathology.

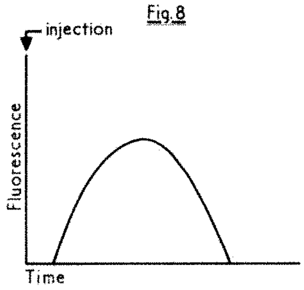


FIG. 8 *Diagram to illustrate intravascular fluorescence of normal iris vessels during first dye transit*

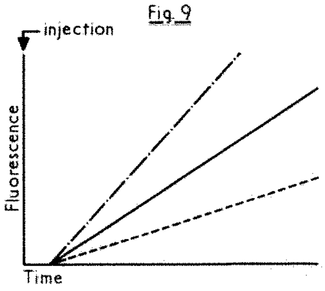


FIG. 9 *Diagram to illustrate extravascular fluorescence of iris stroma due to vessel leak. The gradient of the graph is dependent on iris vessel permeability*

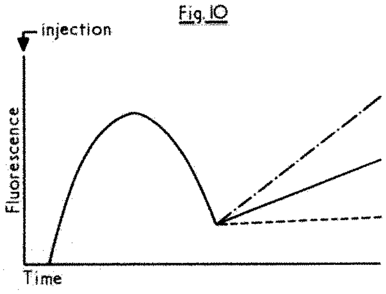


FIG. 10 *Diagram to illustrate biphasic pattern of fluorescence shown by some normal iris vessels,* i.e. *a combination of both intra- and extravascular fluorescence*

Summary

A method of demonstrating the spatial distribution of anterior uveal pathology based on the reaction of normal and abnormal iris vessels to injected fluorescein is described and discussed.

I should like to thank the surgeons of St. Paul's Eye Hospital for access to their patients, and Mr. R. McBride for technical help.

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Ocular effects of chlorpromazine and oxypertine on beagle dogs

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Ocular abnormalities induced by phenothiazine medication have been reported in man (Goar and Fletcher, 1957; Grutzner, 1969; Leinefelder and Burian, 1964; Siddall, 1965; Verrey, 1956) and reproduced experimentally in animals (Cerletti and Meier-Ruge, 1968; McDonald, Snell and Lerner, 1967; Reinert, and Rutty, 1969; Smith, Gavitt, and Karmin, 1966; Wagner, 1956; Weinstock and Scott, 1967). Only a few of the papers published have dealt with electrophysiological changes in visual function (Boet, 1969; Franceschetti, François, and Babel, 1964; Henkes, 1967). In our experiments, we have tried to detect chlorpromazine-induced ocular changes in the dog and to follow their course after stopping the medication. The changes were compared with those possibly induced by oxypertine, a neuroleptic of a different chemical type. Before, during, and after medication we studied the eyes by means of the slit lamp, the ophthalmoscope, electroretinography, histopathology, and biochemical estimations.

Materials and methods

The study was carried out on 24 beagle dogs divided into three groups made up of an equal number of males and females:

(1) eight unmedicated control dogs;

(2) eight dogs treated orally with chlorpromazine for 4 mths, the dosage being progressively increased over 6 wks from 5 to 30 mg./kg./day;

(3) eight dogs treated orally with oxypertine for 4 mths, the dosage being progressively increased over 6 wks from 2·5 to 15 mg./kg./day.

Doses are expressed in terms of base. The animals were medicated 6 days a week by means of an oesophageal probe.

Before beginning medication, all the dogs underwent electroretinographic (Fig. 1, overleaf, p. 410), ophthalmoscopic, and slit-lamp examinations to ensure that they were free from pathological disorders. Ophthalmoscopic and slit-lamp examinations were carried out on conscious dogs, the electroretinogram (ERG) was recorded under pentobarbital anaesthesia. The techniques and parameters of stimulation and recording have been described previously (Rosner and Legros, 1970).

The ERG was recorded during a period of dark-adaptation lasting 30 min.; then the eyes were dazzled for 90 sec. and the ERG was recorded during the following 5 min. Stimulations (150 μ sec. 0·3 Joule) were successively red, blue, and white. We studied the electroretinogram on the one hand in a static manner (in this case the parameter used was the maximum amplitude of the *a* and *b* wave which was obtained during the 30 min. dark-adaptation) and, on the other hand, in a dynamic

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manner (comparison of the curves of dark-adaptation obtained by plotting the amplitude of the *a* or *b* wave against the time of adaptation).

At autopsy one eye of each dog was used for biochemical estimation and the other for histopathology.

Results

I SLIT-LAMP EXAMINATION

Controls and treated dogs were examined 2 and 4 mths after the start of treatment and again 3 mths after the cessation of treatment. No corneal deposits were observed in any of the animals and no opacities capable of modifying the quantity of light received on the retina were detected in the anterior regions of the lens.

II ELECTRORETINOGRAPHIC STUDY

The ERG was recorded in all animals 10 wks and 4 mths after the beginning of treatment then 1, 3, and 5 months after interrupting medication. For each animal the response was taken as the average of the responses given by the right and left eyes. Before beginning treatment it was verified that there was no statistically reproducible difference in the ERG of the different experimental groups.

(1) *Controls*

There was no statistically significant modification in the ERG during experimentation except after 4 mths (Table I), when some changes appeared.

Table I *Electroretinographic changes obtained in a scotopic environment in controls.*

For each recording and stimulation the variations of a *and* b *waves are expressed as a percentage of the initial value.*

The values correspond to the mean of the changes in controls plus or minus the standard error.

Stimulation	*Wave*	*Time after start of experimentation (mths)*				
		2½	4	5	7	9
White	a	+ 0·05 ± 6·0	+25·1 ± 7·1*	−12·0 ± 4·7†	−8·9 ± 11·6	−11·2 ± 12·1
	b	+ 4·7 ± 2·8	+ 8·1 ± 4·8	− 1·1 ± 3·5	−4·9 ± 6·8	− 1·4 ± 1·1
Red	b	+ 9·3 ± 5·3	+21·4 ± 8·1†	− 2·5 ± 5·8	−6·3 ± 8·1	−11·4 ± 6·6
Blue	a	+22·6 ± 15·9	+42·3 ± 12·2*	− 8·4 ± 9·0	−0·06 ± 19·8	− 8·0 ± 10·2
	b	+ 7·7 ± 4·7	+ 8·5 ± 7·1	+ 0·06 ± 6·6	−6·2 ± 5·9	− 3·7 ± 7·4

The values obtained during experimentation are compared to those obtained before the beginning of experimentation with the Student-Fisher test.

Degree of statistical reproducibility: † 0·1 ⩽ P < 0·05 * P < 0·01

(2) *Dogs treated with chlorpromazine*

(*a*) *Static study* (Table II, opposite)

The amplitude of the *a* and *b* waves was diminished in both the treatment and the post-treatment periods. This decrease is statistically insignificant by comparison with the control animals during the medication period and compared with the initial values in the same group for the post-medication period. This latter fact is due to the accentuation of the ERG amplitude decrease in the period free of medication.

Table II *Electroretinographic changes obtained during treatment and after its interruption in a scotopic environment in animals treated with chlorpromazine and oxypertine*

Drug	*Stimulation*	*Wave*	*Time after beginning of treatment (mths)*		*Time after interruption of treatment (mths)*		
			2½	4	1	3	5
Chlorpromazine	White	a	− 7·0 ± 8·0	− 1·3 ± 7·2 ○	−20·1 ± 9·9 △	−28·0 ± 7·1 △	−27·1 ± 10·0 △
		b	−14·0 ± 7·5 ○	− 9·9 ± 7·2 ○	−12·7 ± 6·5	− 6·8 ± 7·5	−13·0 ± 6·2
	Red	b	− 2·0 ± 12·3	− 8·6 ± 8·0 ○	−20·6 ± 7·1 △	−21·0 ± 9·2	−26·7 ± 6·2 ▲
	Blue	a	−16·6 ± 8·4 ○	−12·9 ± 12·1 ●	−27·8 ± 7·7 △	−35·0 ± 8·6 △	−32·6 ± 8·4 △
		b	−12·0 ± 7·9	− 9·8 ± 4·9 ○	−14·7 ± 6·4 △	−13·5 ± 5·8 △	−19·0 ± 3·0 ▲
Oxypertine	White	a	−21·0 ± 5·6 ▲ ○	−10·4 ± 6·4 ●	−21·3 ± 9 5 △	−24·4 ± 4·9 ▲	−12·5 ± 4·8 △
		b	−18·4 ± 5·9 △ ●	−28·2 ± 3·5 ▲ ●	−12·4 ± 5·2 △	−12·7 ± 3·5 △	− 4·7 ± 4·0
	Red	b	−22·6 ± 5·9 ▲ ●	−24·0 ± 4·8 ▲ ●	−21·4 ± 7·5 ▲ ○	−27·7 ± 5·4 ▲ ●	−15·2 ± 5·3 △
	Blue	a	−19·6 ± 8·8 △ ○	− 6·0 ± 14·2 ○	−16·5 ± 15·0	−25·6 ± 7·6 ▲	−16·8 ± 7·5 △
		b	−13·3 ± 6·1 ○	−26·1 ± 2·4 ▲ ●	−15·3 ± 4·7 △	−13·5 ± 3 7 △	− 6·4 ± 4·0

The representation is the same as in Table I. The values obtained during experimentation are compared with those of controls (Mann-Whitney test) and also with those obtained before the beginning of treatment (Student-Fisher test).

Degree of statistical reproducibility:

△ 0·01 ⩽ P ⩽ 0·05	▲ P < 0·01	Student-Fisher test
○ 0·01 ⩽ P ⩽ 0·05	● P < 0·01	Mann-Whitney test

(*b*) *Dynamic study*

The curves of dark-adaptation obtained during the treatment or after its interruption were always below the initial level, but the difference is statistically significant only after the interruption of medication (Fig. 2, opposite). The curves of the dogs treated with chlorpromazine were always below those of the controls (Figs 3 and 4).

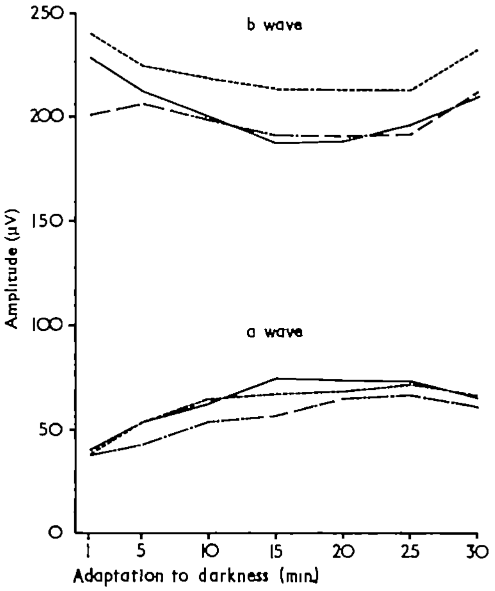


FIG. 1 *Before treatment*

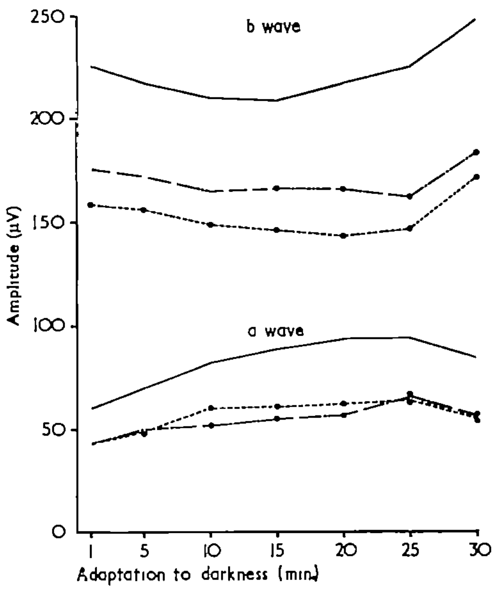


FIG. 3 *After 4 months' treatment*

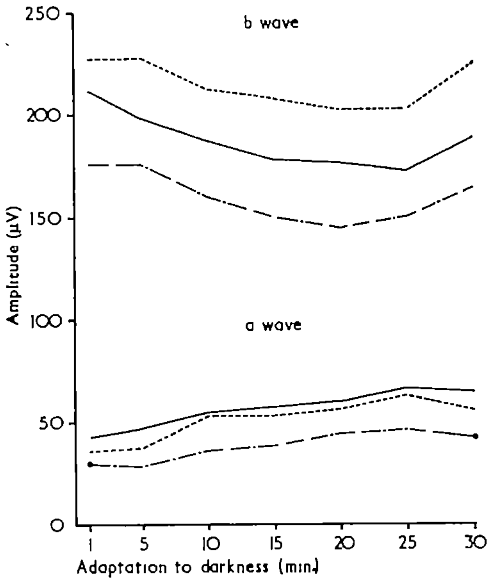


FIG. 4 5 *months after treatment*

FIGS 1, 3, and 4 *Curves of dark-adaptation of the* a *and* b *waves of the ERG* (*white stimulation*) *at different periods of the experiment.*

———————— Control group

– – – – – – – – Group treated with oxypertin

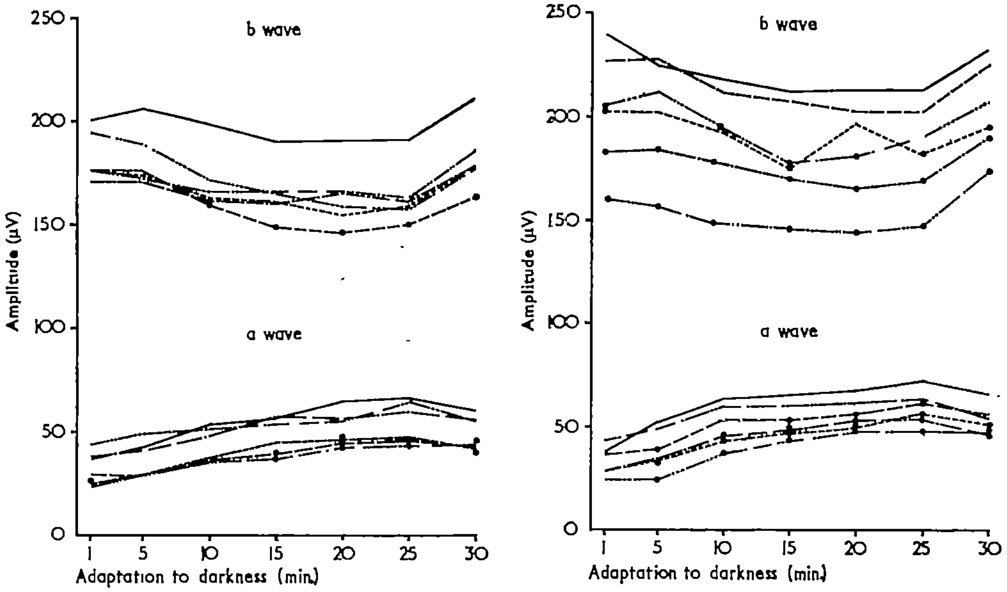
·—·—·—·—· Group treated with chlorpromazine

Level of statistical reproducibility with respect to controls: ● P ⩽ 0·05

(3) *Dogs treated with oxypertine*

(*a*) *Static study* (Table II)

After 10 weeks of treatment there was a statistically significant decrease in the *a* and *b* waves. At the end of treatment, the diminution of the *b* wave became more pronounced, whereas there was an improvement in the *a* wave. After stopping the medication, there was a progressive return towards normal in the *b* wave and after 5 months the difference from the initial level was no longer statistically significant except with the red stimulation. On the other hand, the *a* wave became slightly smaller and the difference was statistically significant. The difference between treated animals and controls observed at the end of treatment disappeared after stopping medication.



FIGS 2 and 5 *Curves of dark-adaptation at different periods of the experiment in the group treated with chlorpromazine* (*Fig.* 2) *and in the groups treated with oxypertine* (*Fig.* 5).

Level of statistical reproducibility with respect to initial value (*before beginning treatment*): ● P ≤ 0·05

————————	Before treatment	- - - - - - - - -	1 month after stopping treatment
—·—·—·—	After 10 weeks' treatment	—··—··—··	3 months after stopping treatment
—··—··—··—	After 4 months' treatment	—— —— ——	5 months after stopping treatment

(*b*) *Dynamic study*

The curves of dark-adaptation obtained during treatment were at a lower level than the premedication curve and the difference was statistically significant. After stopping the medication there was a progressive improvement which was total for blue and white stimulations (Fig. 5). The changes were more pronounced for the *b* wave than for the *a* wave. During the treatment period, the curves of dark-adaptation of the treated animals were below those of the controls and the difference was more often statistically significant. After stopping the treatment there was a progressive improvement and after 5 months they were at the level of, or slightly above, those of the controls (Figs 3 and 4).

III OPHTHALMOSCOPIC EXAMINATIONS

These were carried out just before or immediately after the electroretinographic recordings, and photographs of the fundi were taken; the examiner did not know to which group each dog belonged. With oxypertine, clear changes in the fundus were visible only after 4 months of treatment; there were decreases in brilliance of the tapetum lucidum, conjunctival secretions, and ocular irritation. After medication was stopped all the dogs progressively returned to normal. At the end of the treatment, no change was visible with chlorpromazine except in one dog in which there was a spreading of the green margin; a decrease in the tapetum lucidum brilliancy appeared after stopping the treatment in three out of the seven dogs and persisted in two of these three after 5 months. At this time the green margin between the two tapeta in dogs medicated with chlorpromazine tended to be blue-green while in dogs medicated with oxypertine and in the controls it was emerald green.

IV BIOCHEMICAL ESTIMATIONS

The results are summarized in Table III. As estimations were made 5 months after stopping medication the quantity of drug fixed in the eye was very small except in one dog

Table III *Biochemical estimation of the quantity of drug fixed in the eyes of dogs treated with oxypertine and chlorpromazine*

Medication	*Dog no.*	*Quantity fixed in the eye (μg./g.)*
Control (H_2O)	16	0·0
	28	0·0
Oxypertine	1	2·0
	4	1·2
	5	1·1
	9	1·6
	20	1·6
	25	1·8
	30	2·0
Chlorpromazine	3	1·6
	11	0·9
	15	0·0
	17	1·3
	22	0·0
	27	0·0
	24	13·3
	7*	76·8

*This dog died after 11 weeks of treatment. The eyes were removed immediately after death.

For chlorpromazine estimation the method was spectrophotometry of total phenothiazines; the results are expressed in total phenothiazines in the form of chlorpromazine equivalent (HCl) which gives the same optical density.

For oxypertine estimation the method was fluorometry of total extract. Results are expressed in total fluorescence of various metabolites in the form of the oxypertine equivalent which has the same fluorescence.

treated with chlorpromazine (No. 24). The quantity was far greater in the dog which was still receiving chlorpromazine treatment at the time of its accidental death (No. 7).

V HISTOPATHOLOGY

The eyes of controls and of dogs treated with oxypertine were completely normal on histopathological examination.

In the groups medicated with chlorpromazine, only seven of the original eight dogs could be examined; in the one which died accidentally the eyes showed *post mortem* autolysis. Three of the seven dogs medicated with chlorpromazine exhibited peripheral or central intraretinal cystic formations, some of which were bordered by a lympho-histiocytic infiltration spreading along a dilated vessel (Figs 6 and 7). One showed a marked diffuse congestion of the retinal vascular system.

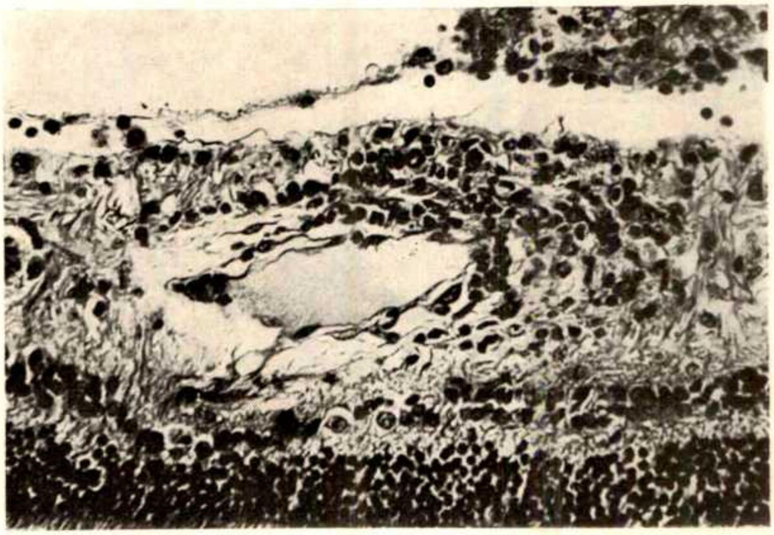


FIG. 6 *Dog No. 11 treated with chlorpromazine. Trichrome stain.* ×350
Retinal granuloma

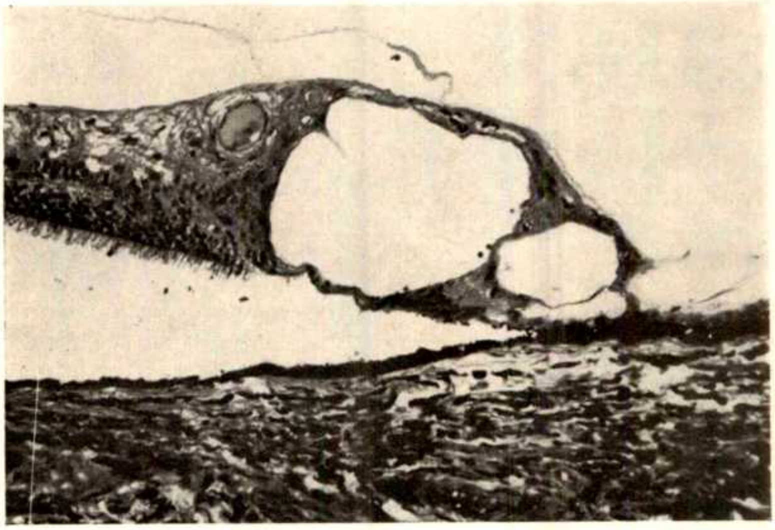


FIG. 7 *Dog No. 11 treated with chlorpromazine. Trichrome stain.* ×175

Discussion

The ratio of the dose levels of oxypertine and chlorpromazine (1 : 2) is very near to the usual therapeutic ratio as well as to that determining an equivalent pharmacological activity (1 : 2·5). Both oxypertine and chlorpromazine administered to dogs at high sub-toxic dose levels are able to induce ocular modifications. No drug or only an extremely small quantity was found in the eye 5 months after stopping medication and this despite the well-described affinity of chlorpromazine for ocular tissues (Mathalone, 1967; Potts, 1962; Potts, 1964; Reinert and Rutty, 1969). These results are quite different from those obtained with quinolines which are eliminated far more slowly from melanin-containing tissues (McChesney, Banks, and Sullivan, 1965). No corneal or lens pigmentation was found in dogs, whereas a deposit of yellowish or brown pigment in the cornea and pigmentation (capsular and subcapsular) of the lens have been described in man during chlorpromazine treatment (Greiner and Berry, 1964; Mathalone, 1967; Petrohelos and Tricoulis, 1969; Siddall, 1965). Histological alterations after phenothiazine treatment have previously been described (Cerletti and Meier-Ruge, 1968) and our results show that in the chlorpromazine-treated group the four dogs with retinal histopathology were those in which the ERG had a diminished amplitude and three of these dogs exhibited fundus changes. Fundus alterations such as pigmentation, pallor of the optic discs, and attenuation of vessels have been reported in man (Boet, 1969; Goar and Fletcher, 1957; Petrohelos and Tricoulis, 1969; Siddall, 1965).

Since ontogenetically the retina is a part of the brain, it is not surprising that drugs acting on the central nervous system also show some activity at the retinal level, which may appear as an undesirable side-effect. Deep reversible or irreversible alterations in the ERG induced by psychotropic drugs on the isolated retina have been described by Lutzow and Hommer (1969).

All potent drugs have their associated side-effects; their presence is obviously important but just as significant is their reversibility after stopping medication. Our data on these two neuroleptics indicate a reversibility for oxypertine-induced ocular changes, whereas those induced by chlorpromazine are not reversible. This situation should be correlated with the fact that no ocular side-effects have been reported after oxypertine treatment in humans.

Summary

Drug-induced ERG and fundus changes due to oxypertine were reversible in dogs after stopping oxypertine administration, but this was not the case with chlorpromazine. The irreversibility of changes due to the latter was associated with the presence of histological lesions.

The authors are grateful to Dr. G. Mottot and Mr. A. Rouquès for their help. They are also greatly indebted to Dr. P. Vergne for his collaboration during the ophthalmoscopic examinations and to Dr. P. Dusserre for his interpretation of the histological slides.

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The Riddoch phenomenon revealed in non-occipital lobe lesions

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Riddoch (1917) described an entity which bears his name, "the Riddoch phenomenon". He observed that while patients with restricted visual fields from occipital wounds could frequently see moving objects, they could not see stationary ones in the affected fields. Riddoch divided his cases into three categories:

(**1**) Those who perceived movement only on the affected side;

(**2**) Those who perceived both moving and stationary objects (but to a different degree);

(**3**) Those with no dissociation between moving and stationary objects.

From his analysis of the visual fields in ten patients with occipital lobe lesions, he concluded that visual functions concerned with the recognition of moving objects and those concerned with the perception of stationary objects are dissociated from each other in the occipital cortex. He considered the absence of this dissociation for a period of several months to be a poor prognostic sign, and postulated that if recovery is occurring after injury the appreciation of movement could be expected to return before the recognition of a comparable stationary object.

Riddoch did not confirm his hypothesis by testing patients with lesions elsewhere in the optic pathway, and while he tested a wide spectrum of lesions due to war injuries, he described no other unique or isolated response characteristics.

This paper reports patients with confirmed lesions in areas other than the occipital lobes who had response characteristics similar to those described by Riddoch.

Case reports

Patient 1, a 55-year-old female, was referred to the Eye Consult Service, Washington University School of Medicine, because of inability to see objects on the right side. This field loss had progressed to a point where she was able to perceive only light and dark on that side.

Examination

The visual acuity was 20/15 in the right eye and 20/25 in the left. The entire ophthalmological examination gave normal results except for the visual fields.

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Goldmann perimetry (Fig. 1) revealed a right homonymous hemianopsia to the I_{2e}, III_{4e}, and V_{4e} test objects in both hemianopic fields. In the parts of the defective field where the patient could see a moving target, she could not see the same target if it was not moving (the Riddoch phenomenon). Because of this, further tests (Sunga and Enoch, 1970) as recently developed by one of us (J.M.E.) were carried out.

These tests not only confirmed that the patient exhibited greater sensitivity to a moving test object than to a stable one, but also demonstrated that the dissociation between moving and non-moving test objects was most noticeable in the corridor between the fovea and the blind spot, and that the kinetic field in the right eye had a tendency to contract on repeated testing.

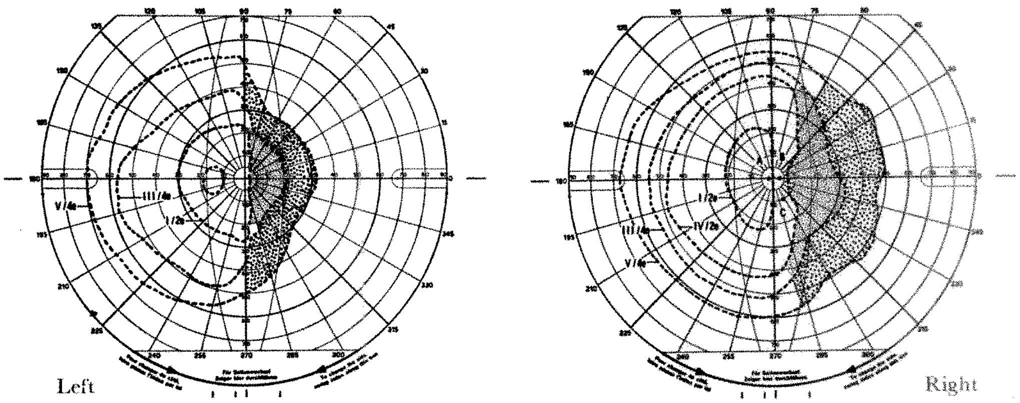

FIG. 1 *Kinetic Goldmann fields illustrating Riddoch phenomenon in Patient 1.*
Points A, B, and C illustrate where repeat flashing static thresholds were determined by J.M.E. (see Fig. 4)

A repeat flashing static perimetric test was performed using the test technique recently introduced by Sunga and Enoch (1970) (see Addendum). The patient experienced rapid loss of sensitivity to stationary flashing targets as a function of time in affected field areas. Comparable findings have been observed in lesions ranging from optic neuritis to occipital abnormalities (a phenomenon believed to be related, in part, to that described by Riddoch).

On the basis of the right homonymous hemianopsia, the positive Riddoch phenomenon, and the gradual progression by history, a mass lesion in the left occipital lobe was suspected. Neurological examination, skull films, and electroencephalogram were all within normal limits. A lumbar puncture was normal except for a cerebrospinal fluid protein of 60 mg./per cent. A left carotid arteriogram revealed a large aneurysm of the internal carotid artery distal to the bifurcation, with an intact posterior cerebral artery coming off the anterior circulation.

Operation

A large aneurysm of the left internal carotid (2 × 3 cm.) was noted to be compressing the left optic tract which was described as "thinned and discoloured". As in the arteriogram, there was no evidence of compression of the posterior cerebral artery.

Patient 2, a 38-year-old male, presented with a complaint of decreased visual acuity in both eyes, with greater loss in the right eye. He had first noticed decreased vision in the right eye in 1965, when he consulted an ophthalmologist who told him that a "blocked blood vessel" was responsible for the visual loss; and 3 months before he was seen in our office, the vision in the left eye had decreased from 20/20 to 20/30.

Examination

The visual acuity was counting fingers in the right eye and 20/30 in the left. The right pupil exhibited a Gunn phenomenon. Funduscopic examination showed bilateral optic atrophy, much greater on the right side.

Goldmann perimetry (Fig. 2) revealed a bitemporal hemianopsia with a positive Riddoch phenomenon to a V_{4e} test object in the temporal field of the *left* eye only.

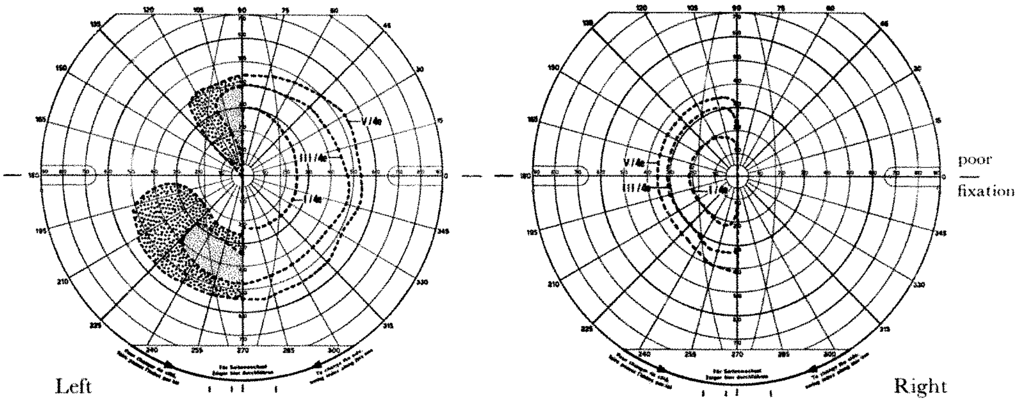

FIG. 2 *Preoperative fields, showing field defect in Patient 2, who showed then Riddoch phenomenon only in left eye*

Skull *x* rays showed an enlarged sella turcica. A right carotid arteriogram was felt to be compatible with a tumour in the suprasellar region with anterior extension.

Operation

The optic chiasm was displaced by a large tumour mass and the right optic nerve was compressed and thinned. Postoperative Goldmann perimetry (Fig. 3) showed a positive Riddoch phenomenon in *both* temporal fields to the III_{4e} and V_{4e} test objects.

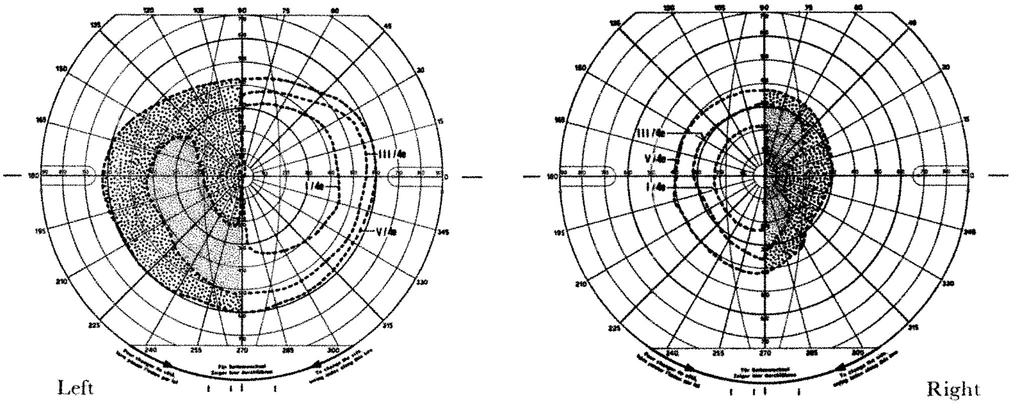

FIG. 3 *Postoperative fields of Patient 2, who then displayed bilateral Riddoch phenomenon*

Comment

Walsh and Hoyt (1969) list dissociation of visual perception (Riddoch) under the subheading "Topical Diagnosis of Lesions involving the Optic Radiations and Visual Cortex". Riddoch's hypothesis, however, involved only the visual cortex—not the optic radiations or prestriate area.

Recent extensive neurophysiological evidence (Hubel, 1967) does, indeed, suggest separate loci for different visual functions in the occipital cortex. Riddoch's sign, however, is not pathognomonic for an occipital lobe lesion, nor does it carry the prognostic significance that Riddoch attached to it—as evidenced by the two patients we have described and the pathology they demonstrated.

One could hypothesize that, rather than demonstrating a separation of function, Riddoch's data demonstrate that the response to a moving test object is more resistant to loss than the response to a stationary target. There may be some relation between the Riddoch phenomenon and previous studies in local adaptation (Bay, 1953; Cibis, 1947, 1948) and, more recently, in the work of Enoch and Sunga (1969) and Sunga and Enoch (1970) with repeat static perimetric testing in lesions of the optic pathway.

Summary

Riddoch (1917) described the dissociation in perception between stationary and moving objects in patients with occipital lobe lesions from war injuries, and commented on the prognosis of patients with field loss who demonstrated this phenomenon. This communication describes two patients with progressive lesions elsewhere in the visual pathway who demonstrated the Riddoch phenomenon, thus showing that the Riddoch phenomenon is not pathognomonic for occipital lobe or optic radiation lesions.

ADDENDUM

REPEAT STATIC FLASHING PERIMETRIC TEST (Fig. 4).

In this test (Enoch and Sunga, 1969; Sunga and Enoch, 1970) the patient is given 5 or more minutes' rest with the eyes closed while sitting in front of a quantitative perimeter. Then, after taking up fixation, he judges the presence or absence of a repeatedly flashing test target located at a predesignated test point in the field. The static threshold is determined again and again for a 5-minute

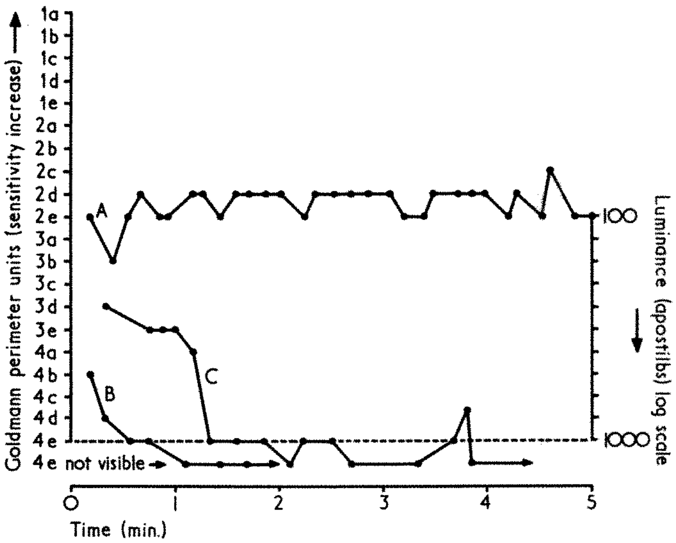

FIG. 4 *Repeat flashing static perimetric test utilizing Points A, B, and C, in the right field of Patient* 1. *Data have been plotted in terms of visual sensitivity* (1/*threshold*). *Perimeter background* 31·5 *apostilbs. Target luminance given on ordinate to right* (*increasing downwards*).

Usual designation of stimulus magnitudes available on Goldmann Haag-Streit perimeter given on ordinate to left. Here the threshold to a periodically presented non-moving stimulus has been determined. The same test is repeated again and again during a 5-*min. test period* (*Sunga and Enoch*, 1970; *Enoch and Sunga*, 1969).

4*eNV signifies that even an* 1000 *apostilb target* (100 *millilamberts*) *was "not visible" to the patient.*

period at this point. The light is flashed in order to distinguish a saturation or fatigue-like effect from a local adaptation anomaly.

The first patient referred to above was tested initially at *Point A* (Fig. 1) in the normal part of the field, using a Goldmann size 0 target presented for 70 msec. every half second. In Fig. 4, we see that *Curve A* gives a relatively stable, normal response throughout the 5-minute test session. Repeating the test at *Point B* (Fig. 1), a Goldmann size V target was required! A marked decay in sensitivity was noted at this point (Fig. 4). The test was repeated at *Point C* (Fig. 1), using a Goldmann size IV target. At this locus, the initial sensitivity was higher, but it again fell off sharply in time (Fig. 4). 4*e NV* in Fig. 4 signifies that the brightest target in the Goldmann perimeter (1,000 apostilbs) was no longer visible.

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Penetrating thistle bracts injury

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Penetrating corneal injury, which is one of the commonest ophthalmic casualties, may be caused by industrial and road traffic accidents, assaults with sharp instruments, animal scratches and bites, and agricultural mishaps. In the last group, perforation of the eye by thorns and twigs frequently occurs in such activities as bush-cutting and hedge-trimming.

Case report

An 8-year-old boy was admitted to the West of England Eye Infirmary with a history of having been hit in the left eye by the prickly flower base of a thistle 2 days previously. His father had hit a thistle plant with a stick and the decapitated flower base had struck the boy's eye. No discomfort was felt until 2 days later when increasing irritation made him attend at the hospital.

Examination

Three prickles about 2 mm. long were embedded in and penetrating the full thickness of the cornea. They were stiff, fine, and like needle-tips; their bases were flush with the corneal epithelium, and the shafts traversed the full corneal thickness with the pointed end protruding 1 mm. into the anterior chamber. The positions of two of the prickles are visible in Fig. 1, the third being hidden under the upper lid. The anterior chamber was normal in depth and no aqueous leak was demonstrable by Seidel's test as all the wounds were plugged water-tight by the prickles. The pupil was 3 mm. in diameter with a normal reaction. There was slight conjunctival injection and only a few cells were visible in the anterior chamber on slit-lamp examination. The visual acuity was 6/6 in the right eye and 6/9 in the left. There was no evidence of any damage to the lens and the fundus was normal.

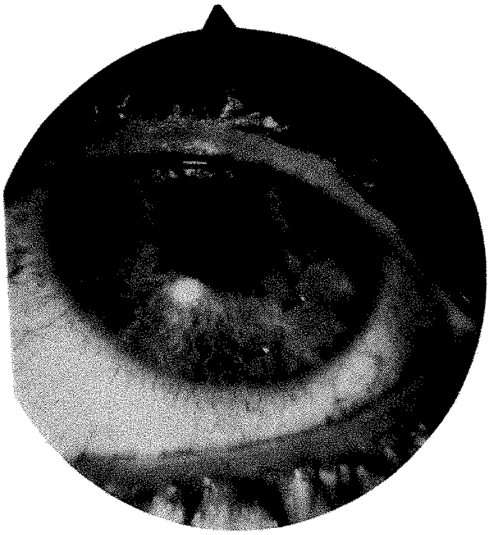

FIG. 1 *Two thistle prickles sticking into the cornea*

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Management

Under general anaesthesia and using an operating microscrope, one prickle was picked out with Colibri forceps. Aqueous fluid immediately gushed through the wound and the anterior chamber was lost. The remaining two prickles could not be picked out in a similar manner as the anterior chamber had collapsed and any pressure on the base of the prickle through grasping it, could have resulted in damage to the lens by the sharp end in the anterior chamber. The anterior chamber was, therefore, re-formed by placing a Rycroft's cannula over the mouth of the wound and injecting saline. The second prickle was removed in a similar manner and again the anterior chamber collapsed through leakage of aqueous. The anterior chamber was again replenished by injecting saline through the second wound; the third prickle was then picked out and the anterior chamber was again lost, but re-formed by the same process using a Rycroft's cannula. After this procedure the patient had a deep anterior chamber and three sealed tracks were visible in the cornea. Finally, soframycin was injected subconjunctivally.

Results

Postoperative recovery was uneventful and the corneal wounds healed satisfactorily, leaving minute scars. The patient was discharged 6 days later with visual acuity 6/6 in both eyes unaided.

Discussion

Ocular damage inflicted by vegetable matter may be of variable severity from mild local conjunctival reaction to the loss of an eye (Duke-Elder, 1954). Goodwin (1968) described burdock ophthalmia due to burdock shafts which are typically embedded vertically in the upper fornix with the tip protruding and causing corneal abrasions. Nodular conjunctivitis due to burdock (Hartmann, 1940) and thistle-down (Jakowlewa, 1924) has also been described. Paddy grains flying up when rice is threshed with sticks may give rise to corneal abrasions (harvest ulcer) due to the spiky hairs of the paddy husks (Joseph, 1968). Injury of a serious nature, not infrequently ending in blindness, may be caused by the penetration of the mesquite thorn, which secretes a wax containing cerotic acid which is an irritant to the eye (Brunner and Bieberdorf, 1950). Penetrating wounds by aloe barb may also cause toxic iridocyclitis and take a severe course (Sédan and Roucher 1956). The penetrating injury described above, which was caused by the hard prickles of the spear thistle, took a relatively benign course.

The spear thistle (*Cirsium lanceolatum*) belongs to the family Compositae and grows abundantly in fields and pastures, and on waste ground. The flowers are crowded into heads (capitula) and surrounded by the flower base (involucre); the latter, as shown in Fig. 2, is composed of rows of numerous bracts, all narrow and ending in sharp hard prickles (Hutchinson, 1955; Butcher, 1961). Three such prickles were embedded in the cornea, the impact of the flying involucre having caused the penetration. The nature of

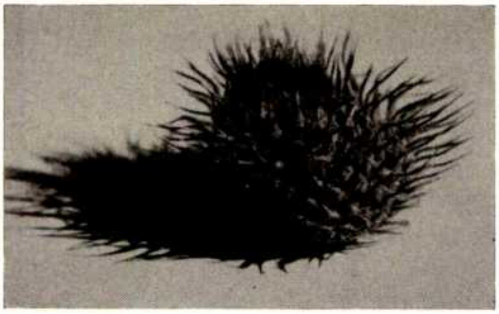

FIG. 2 *Appearance of prickly base of thistle head*

these prickles, apart from causing mechanical injury, seems to be innocuous, as for 2 days they were embedded in the cornea and protruding into the anterior chamber without provoking any marked reaction or uveitis, or even any great discomfort to the patient.

Summary

A case of multiple penetrating injuries by thistle bracts has been reported. Three prickles were embedded in the cornea with the sharp tips protruding into the anterior chamber and the measures adopted for their removal are described. The embedded prickles were innocuous to the eye apart from causing mechanical injury.

I wish to thank Mr. F. J. Rutter for permitting me to manage and report this case and Mr. W. J. Rich for his valuable advice.

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Brit. J. Ophthal. (1971) 55, 424

Blue sclerae with keratoglobus and brittle cornea

N. D. GREGORATOS, C. S. BARTSOCAS, AND K. PAPAS
Aghia Sophia Children's Hospital, Athens, Greece

Blue sclerae are usually found in association with inherited disorders of the mesodermal tissues. They are a consistent sign of osteogenesis imperfecta, but they are also present in the Ehlers-Danlos syndrome and Marfan's syndrome. We report another hereditary condition of blue sclerae associated with keratoglobus and brittle cornea, possibly representing a new syndrome.

Case report

A 4-year-old boy was admitted to the Aghia Sophia Children's Hospital because of a perforating injury of the right eye after a minor accident.

The corneo-scleral wound was large, and during the operation, which was performed immediately the cornea was found to be very fragile and thin, making suturing extremely difficult. The wound re-opened once, but finally healed.

Examination

Both eyes were large and bulging, the sclerae were blue, there was keratoglobus and central corneal opacities (2 to 3 mm. in diameter). The cornea of the left eye was 12 mm. in diameter and the intraocular pressure was within normal limits when measured on several occasions. The fundus was not visible.

History

This was unremarkable except for an arrested hydrocephalus with no abnormal central nervous system signs or mental retardation. Psychomotor development was normal for the patient's age.

Family history (Figure)

The father was 33 and the mother 25 years old. The father was healthy. The mother, who had slightly blue sclerae, had had three pregnancies; the first child was a stillborn girl, the second was the proband, and the third was a 3-year-old girl with blue sclerae.

There was parental consanguinity in that the parents were second-cousins. All members of the family were dark-haired. Absence of bone fractures or deafness or any significant family history or clinical signs excluded osteogenesis, the Ehlers-Danlos syndrome and Marfan's syndrome.

Discussion

The present case appears to represent a hereditary disorder characterized by blue sclerae, keratoglobus, and brittle cornea. A combination of blue sclerae with brittle cornea and red hair was described as a syndrome by Stein, Lazar, and Adam (1968) from Israel.

This Greek family included two children with blue sclerae, one of them also having brittle cornea and keratoglobus. The parental consanguinity suggests an autosomal recessive pattern of inheritance, such as that found by Stein and others (1968), whose large

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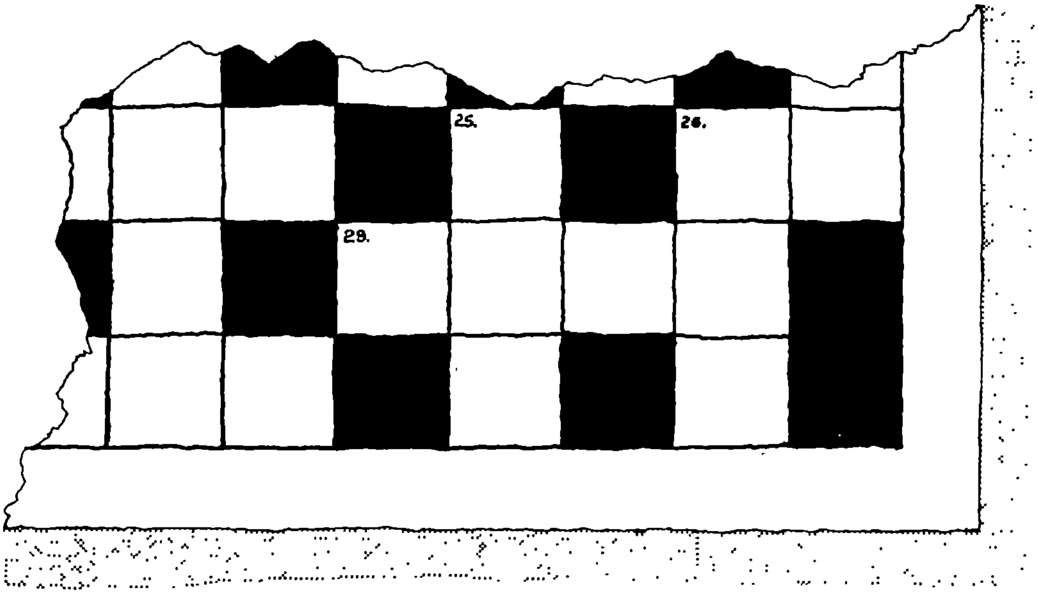

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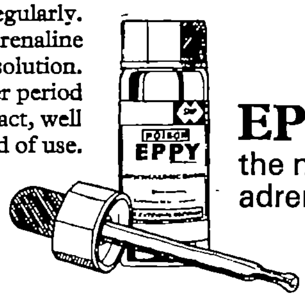

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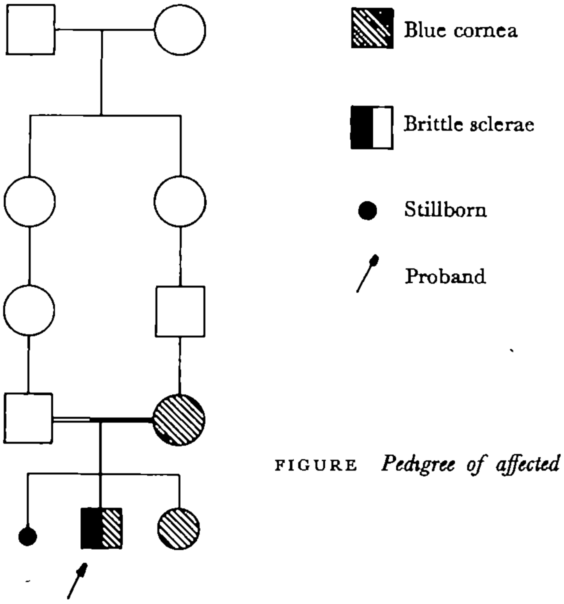

FIGURE *Pedigree of affected family*

pedigree showed brittle corneae in males, while the females had blue sclerae only. In our family there were only the two children affected, but the boy had brittle cornea and keratoglobus, while the female had blue sclerae only. This may suggest a predisposing factor leading to brittle corneae in males only, but does not exclude an X-linked pattern of inheritance.

The large extension of the perforating wound, and the difficulty in suturing, were the result of the thin and brittle cornea and sclera. Duke-Elder (1964) quoted Buchanan's estimation that, in blue sclerae, the thickness is reduced to one-third of normal and that of the cornea to three-fifths of normal. Ruedemann (1953) stated that the chief histological finding in cases with blue sclerae was a thinning and breaking-down of the collagen.

Arkin (1964), referring to the appearance of keratoglobus, stated that he had found only two references describing the co-existence of keratoglobus with blue sclerae (Tucker, 1959).

Keratoglobus often creates diagnostic difficulties. In megalocornea the only change occurs in the dimensions of the cornea, but in keratoglobus there are changes in the thickness and appearance of the cornea.

Badtke (1941) reported the presence of blue sclerae with keratoconus. In keratoconus the thinning involves mainly the apex of the cornea, but in keratoglobus the whole cornea is involved.

The enlarged eyes and the corneal opacities could be diagnosed as buphthalmos, but the absence of increased intraocular pressure, tears in Descemet's membrane, and corneal oedema favour the diagnosis of keratoglobus.

Summary

A Greek family is described in which the mother and two children had blue sclerae. The older child, a boy, also had brittle cornea with keratoglobus. Parental consanguinity was present, and an autosomal recessive pattern of inheritance or an X-linked gene, because of the mother's blue sclerae, is suggested as the cause of this syndrome.

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Self-inflicted orbitocranial injury with a plastic ballpoint pen

D. I. BOWEN

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Self-inflicted ocular injuries are not unusual in psychologically disturbed patients, but only very rarely is a suicide attempt made by stabbing through the orbit. The patient, whose history is reported here, drove a ballpoint pen through the wall of his orbit into the intracranial cavity in a bout of depression, and not only survived but retained fairly good vision. He was probably attempting suicide, though an ocular injury may have been his sole intention.

Case report

A 44-year-old shopkeeper was admitted to hospital in a drowsy state after taking an overdose of phenytoin and phenobarbitone, which he had found in his sister's medicine cabinet. He had been depressed for about 2 years. He recovered rapidly from the overdose, but he was retained in the general ward rather than transferred to the care of the psychiatrists because he had a persistent low-grade pyrexia, which was probably related to pulmonary shadows seen at both apices on chest *x* ray. During this period he was depressed and tearful.

He was found unconscious in the ward bathroom 5 days after admission. Examination revealed right-sided spasticity and lumbar puncture showed uniform blood-staining of his cerebrospinal fluid. A diagnosis of cerebrovascular accident was made, but was soon revised when a straight *x* ray of the skull (Figs 1 to 3) revealed a ballpoint pen (Fig. 4) within the cranial cavity. The pen had apparently been thrust through the right orbit across the midline of the head into the left temporo-occipital region, and the *x* rays suggested that the end of the pen might still be present in the orbit.

Operation

Under general anaesthesia, therefore, an ophthalmologist explored the orbit, while a neurosurgeon stood by in case any intracranial manoeuvres became necessary. Conjunctival tears were found in both medial canthi suggesting that an attempt had been made to push the pen into the left orbit before succeeding on the right side. 1 cm. of the hilt was found in the orbit with the rest beyond a hole in the ethmoid bone. The pen was withdrawn through the orbit, while the neurosurgeon stood ready to apply carotid compression. A gush of cerebrospinal fluid followed, but there was no haemorrhage.

Progress

Postoperatively he was treated with systemic chloramphenicol and his condition gradually improved over the next 2 days. He became accessible to simple commands, and movements began to return in the right arm and leg. A week later, however, neck stiffness developed, and, although the cerebrospinal fluid was sterile, the level of consciousness deteriorated. There was also a profuse cerebrospinal leak from the right nostril.

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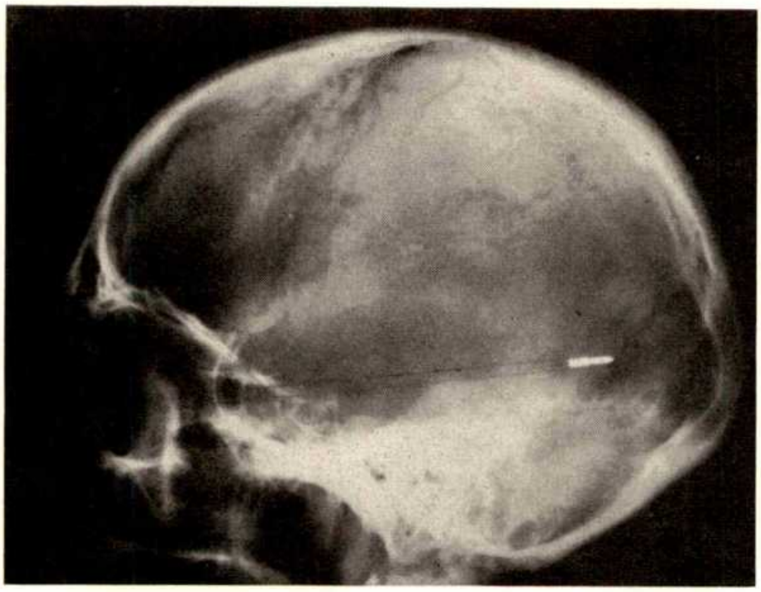

FIG. 1 *Radiograph of skull, lateral view*

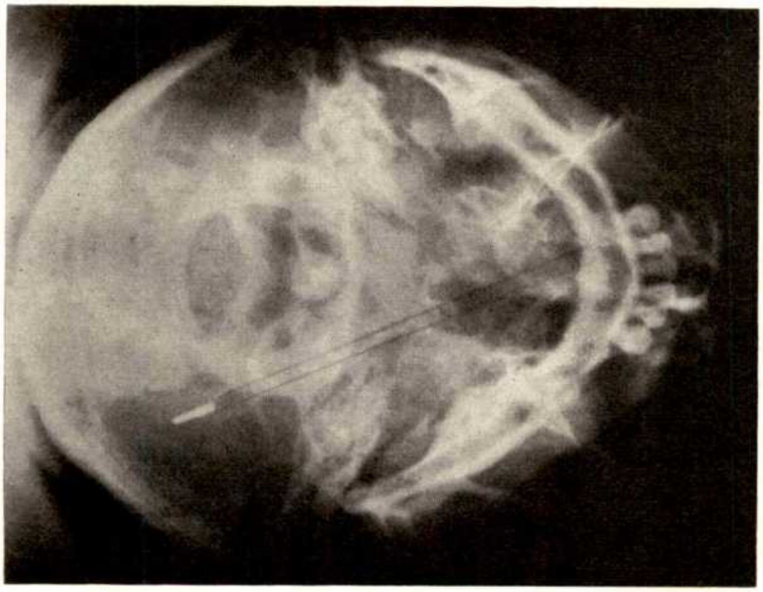

FIG. 2 *Radiograph of skull, basal view*

Second Operation

Intracranial exploration was clearly indicated and 9 days after the first operation a right frontal craniotomy was carried out through four burr holes. It was found that an aerocele had developed in the subdural space and was compressing the brain. There was a large hole in the jugum sphenoidale in the midline exactly between the two optic nerves and a few fragments of bone were lying loose in the opening. A plug of muscle was pushed into the hole and covered with pericranium taken from the bone flap.

Result

The patient's condition improved steadily after this procedure, and he was transferred to a psychiatric hospital 16 days after the second operation.

(3)

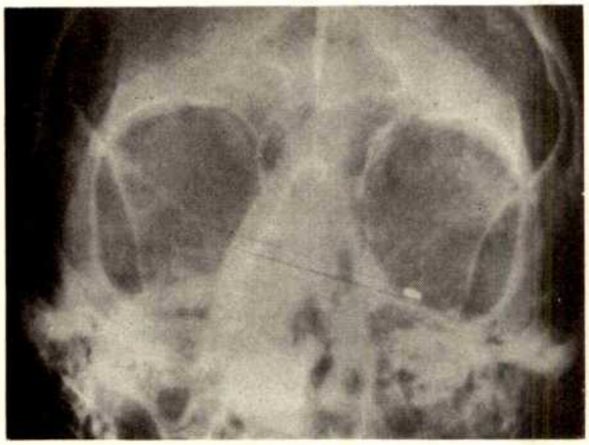

FIG. 3 *Radiograph of skull, antero-posterior view*

(4)

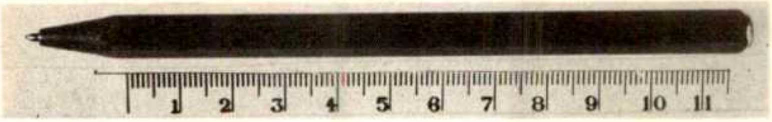

FIG. 4 *The ballpoint pen (cm)*

Follow-up

2 years later he was cheerful, cooperative, and alert, and was living at home. He said that he had no recollection of his injury or of his stay in the Neurosurgical Unit, but he knew what he had done to himself. He had found this out when he was being examined by some students and his wife had filled in the details. He was well adjusted to his right hemiparesis and was able to walk without too much difficulty with the aid of leg calipers. The right arm and hand, however, were not much use to him, and he volunteered the information that his sense of smell had been poor since his injury.

The visual acuity was 6/9 part in the right eye, with −16 D sph., −2 D cyl., axis 50°, and 6/5 part in the left eye, with −3·25 D sph., −3 D cyl., axis 145°. Ocular movements were full and the pupils equal, but their reaction to light was sluggish on both sides. The left disc was pale and atrophic and the visual field grossly contracted. The right fundus showed the characteristic temporal disc crescent and atrophic posterior pole associated with high myopia, but the disc itself had a good colour and the right visual field showed no gross changes. Both intraocular pressures were normal. There was slight diminution of pin-prick sensation in the distribution of the first and second divisions of the right trigeminal nerve, but both corneal reflexes were normal. Facial movements were full and speech normal. Examination of the limbs showed a marked right spastic hemiparesis.

Comment

2 years after the injury this patient shows the following abnormal neurological signs: minimal right trigeminal neuropathy affecting the upper two divisions, left optic atrophy with contraction of the left visual field, anosmia, and a right spastic hemiparesis. The pen is known to have entered the right ethmoid bone in the orbit, emerged into the cranial cavity through the jugum sphenoidale, and passed backwards, upwards, and laterally for a distance of some 9 cm. The pen, therefore, in its course must have injured the olfactory tracts, the intracranial portion of the left optic nerve, and the left cerebral peduncle. The right trigeminal neuropathy is more difficult to explain, although some branches of the ophthalmic division may have been injured by the pen in the orbit.

The patient had no recollection of his injury and it is not possible to say with any certainty whether he was trying to take his own life or to injure his eyes. Self-inflicted ocular injuries are not unusual in psychotic patients and are often severe. Chemical burns of the conjunctiva and cornea (Duke-Elder, 1954), penetrating wounds of the globe (Byrnes and Shier, 1949; Riebel, Anton, and Kumstát, 1961), and self-induced solar retinopathy (Anaclerio and Wicker, 1970) are some of the means by which such patients harm their eyes. The most violent injuries on record are autoenucleations. Davidson (1962), in a study of self-mutilation, found in the literature eight patients who had torn out both their eyes, and more recently Gorin (1964) and Malevitis, Arapis, and Stamatinis (1965) described two further instances of autoenucleation in psychotic patients. It is possible that the patient whose history is reported here was motivated in a similar manner, although suicide was probably his objective. Albert, Burns, and Scheie (1965) reported the case of a psychotic patient who attempted suicide by thrusting a 6-in. pencil through his upper lid, orbit, and sphenoidal fissure into the intracranial cavity. Treatment consisted of a fronto-temporal craniotomy with removal of the pencil *via* the orbit, and a total ophthalmoplegia and optic atrophy with blindness on the affected side resulted from the injury. This is the only report found in the recent literature which resembles the case presented. A final possibility is that of an accidental injury in which the patient fell while holding the pen close to his eye. This seems unlikely because the end of the pen was found deep in the orbit and also because of the conjunctival lacerations in the opposite eye.

Summary

A patient thrust a plastic ballpoint pen through the wall of his right orbit into the intracranial cavity in a bout of depression. The pen was removed *via* the orbit and the subsequent management is described. The injury resulted in left optic atrophy, anosmia, and a right spastic hemiparesis.

I wish to thank Mr. R. D. Weeks and Mr. P. A. Graham for their advice and for permission to examine their patient.

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Book reviews

Visual Perception. By T. N. CORNSWEET. 1970. Pp. 475, figs. Academic Press, New York and London. (£7.00)

This book has the advantage of having been written by a research worker in vision who has taught at Yale and at Berkeley, California. It is a very good book indeed with a sound theoretical basis, and one in which the explanations are exceedingly lucid. The style is lively, and in places humorous, and this makes it easy reading. It is aimed at bright undergraduates and graduate students and, although it leans heavily on physical and physiological concepts, it is written for a general readership and not necessarily for those who have previously studied these two disciplines. It would be of great interest to physicists, psychologists, engineers, and biologists who need to know more about the present state of visual knowledge and some research problems.

The reader is advised to read the book through as one would a novel (many novels are far less exciting) and to skim rather than skip if one must.

No subject is more fascinating or important than visual perception. Most of one's information input is visually processed, but it is an absorbingly interesting subject for two main reasons. First, the information from the eyes goes straight to the brain where it is "perceived" and little is yet known about the act of perception. Secondly, even the anatomy and physiology of the eye and the visual pathways are not by any means properly understood and, although knowledge is accumulating very rapidly, there is still a great deal we do not know. This makes it even more intriguing.

After an introduction, the book begins with an account of the work of Hecht, Schlaer, and Pirenne on flash stimuli, explaining that the human visual system has the ultimate sensitivity, in other words it can detect a single light quantum. Chapters then follow on the physics of light, quantal fluctuations, and the rod and cone pigments and their excitation by light. Then there are chapters on colour vision which occupy about a quarter of the book.

After this the book becomes more specialized, and specific problems of particular interest to the author are dealt with in some depth. These include the psychophysiology of brightness, brightness and colour constancy, spatial interactions, temporal aspects, and visual modulation transfer functions, which are discussed both spatially and temporally. The two final chapters are on stimulus generalization and on speculation on "higher processes", which is mainly a discussion on why inhibition has evolved. These parts are excellent, stimulating, and very well written, but they do limit somewhat the usefulness of the book as a general text since many visual phenomena are not mentioned at all. This is not meant to understate the value of the way in which the subjects included are introduced and described, and particularly noteworthy are the sections on the visual modulation transfer functions, which is the best account the reviewer has seen in any book.

One or two points of criticism can be mentioned, although none is very serious. The transmission of a nerve impulse by an action potential is not well explained and a diagram would have been helpful. Also it is surely less misleading to speak of "colour defectiveness" than of "colour blindness", since very few people indeed are completely devoid of any colour sense. Furthermore, to state that "the normal human visual system is extremely colour blind" is even more misleading, when simply describing the fact that one cannot distinguish a red plus green mixture from a monochromatic yellow.

The pedagogic advantage is questionable of presenting colour mixture data in a novel way, on a vector diagram in terms of quanta of light absorbed by the three visual colour processes. A few C.I.E. eyebrows will, no doubt, be raised to find that their favourite brainchild appears only in a swollen footnote.

Almost all the topics discussed in this book can be explained on a physiological basis, and the author thinks that, in time, every phenomenon will be found to have such a basis. He tends to play down the role of perception and, in doing so, conveniently omits any mention of such common phenomena as size constancy, or the moon illusion, in which "*perception*" obviously plays a vital part. This is a pity, especially since the title of the book is "Visual *Perception*".

The book is designed in a modern idiom with very wide margins. At the most only 43 per cent. of the page area contains print, and at the least only about 14 per cent. The book therefore seems more expensive than necessary, since one is paying a lot for the wide-open spaces. It is profusely illustrated with many very clear diagrams with long explanatory captions, and with many black-and-white and some colour photographs. One has, of course, to put up with American spelling, although it is a little difficult to accept "aberration" spelt consistently with two "b's" and one "r" as other than a mistake.

Colour Blindness. An Evolutionary Approach. By R. CRUZ-COKE. 1970. Pp. 156, 40 figs, bibl. Thomas, Springfield, Ill. ($8.75)

The author has approached his subject from the point of view of "biological" evolution. To a large extent the work consists in a survey of the literature.

Obituary

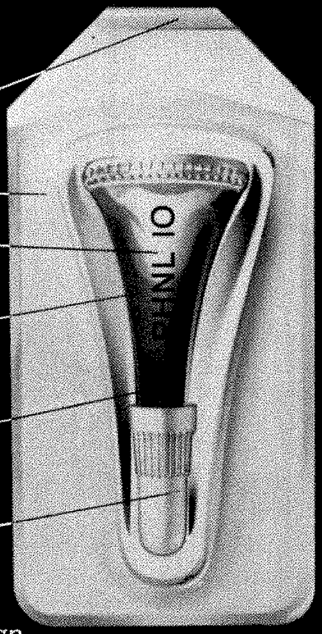
Howard Vincent Coverdale, 1897–1971

Howard Coverdale, who was one of the most pleasant, companionable and likeable and, at the same time, most efficient of the ophthalmologists to be trained in Britain, subsequently became one of the foremost ophthalmic surgeons in New Zealand where his influence was immense.

Coverdale was born in Christchurch in the South Island of New Zealand. After leaving school where he became head-prefect, he learned to fly at Auckland and joined the R.A.F. in England in 1918. On his demobilization at the end of the war he went to Cambridge University and his versatility was immediately apparent in his becoming president of the Medical Society, president of the Heitiki Club (of New Zealand men at Cambridge), and a member of the Shakespeare Club of Caius College, and representing his college at tennis, golf, and hockey. His medical education was completed at St. Thomas's Hospital, London, where his athletic ability made him captain of the tennis and golf teams. His main interest, however, was ophthalmology, and for this reason he went through the residency at Moorfields Eye Hospital. Here he excited the greatest regard and affection; indeed, because of his surgical skill and personal qualities, he was one of the most popular residents the hospital has had. Despite the fact that he was pressed to remain in London, he decided to return to New Zealand, largely for reasons of health, and set up ophthalmic practice in Auckland.

Here, as would be expected, he prospered; but on the outbreak of the second world war he immediately enlisted in the army and, going overseas with the Third General Hospital, he was responsible for most of the ophthalmology in the New Zealand Division – and for many others – in the North African and Italian campaigns. Returning home in 1945, he maintained his interest in the Services by becoming chairman of the Medical Committee of New Zealand St. Dunstans with which he worked for many years.

His contributions to our specialty were considerable and, in addition to numerous papers on a wide variety of subjects in various medical journals, he was editor of the *Transactions of the Ophthalmological Society of New Zealand* for 10 years, an associate editor of *Ophthalmic Literature*, and a member of the International Editorial Board of the American Quarterly Review of Ophthalmology. In the profession in his own country the esteem in which he was held was shown by his occupying the posts of president of the Ophthalmological Society of New Zealand and of the Auckland Clinical Society. Outside his profession his interests in the arts, architecture, and the cultivation of trees and shrubs occupied much of his attention, as well as racing and golf. His death brings sorrow to his many friends in Britain and in his own country where an immense blank is created. To his widow, Margaret, our sincere sympathy is extended.



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EYE INJURIES *by* **Edward Zagora,** *Univ. of Sherbrooke, Canada.* Discusses incidence, etiology, pathology, diagnosis, prognosis, prophylaxis, and treatment for most conditions. Chapters on posttraumatic plastic surgery are presented as a compilation of operations which have proven to be successful in the authors' hands. Substantially concerned with ocular symptoms associated with neurological and neurosurgical conditions due to trauma. Clinical photographs, fundus photographs, drawings, diagrams, and tables supply abundant illustrative material to supplement the text. '70, 618 *pp.* (7 × 10), 375 *il.*, 4 *tables*, $30.75

CORNEAL AND EXTERNAL DISEASES OF THE EYE: First Inter-American Symposium *compiled and edited by* **Frank M. Polack,** *Univ. of Florida, Gainesville.* (54 *Contributors*) Covers diagnosis and treatment of bacterial, viral and fungal infections of the cornea, parasitic infections of the eye and its treatment, up-to-date status of epikeratoprosthesis and soft contact lenses in the treatment of corneal diseases, keratoprosthesis—its scope, techniques, and complications, problems in corneal grafting, and microsurgery. '70, 400 pp. (6¾ × 9¾), 217 *il.* (2 *in full color*), 46 *tables*, $24.00

CONTACT LENS MEDICAL SEMINAR: Volume I. Proceedings of the First Biennial Contact Lens Medical Seminar Held in Conjunction with the Annual Meeting of the American Academy of Ophthalmology and Otolaryngology. *Edited by* **Whitney G. Sampson** *and* **Gerald L. Feldman.** *Foreword by* **Joseph M. Dixon.** *Introduction by* **Abraham Schlossman.** (10 *Contributors*) Covers fundamentals as well as clinical applications of corneal physiology, control and management of optical problems, selected fitting problems, and scleral lenses. Emphasis is on adapting basic procedures to office practice. '70, 192 *pp.*, 31 *il.*, 17 *tables*, $10.50

SO YOU HAVE CATARACTS: What You and Your Family Should Know *by* **Albert E. Sloane,** *Harvard Medical School, Boston.* To save time for the physician by answering often-asked questions by the patient, and motivate the patient to continue treatment. Includes a narrative sequence of the natural history of a cataract from onset until after surgery and its correction with glasses or contact lenses. "Hundreds of ophthalmologists and thousands of patients will have cause to rise up and bless the name of Dr. Sloane for this useful book"—Archives of Ophthalmology. '70, 106 *pp.*, 5 *il.*, $5.75

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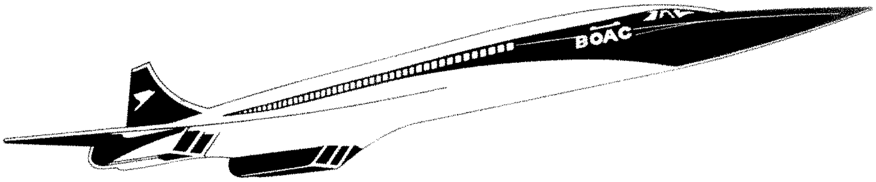

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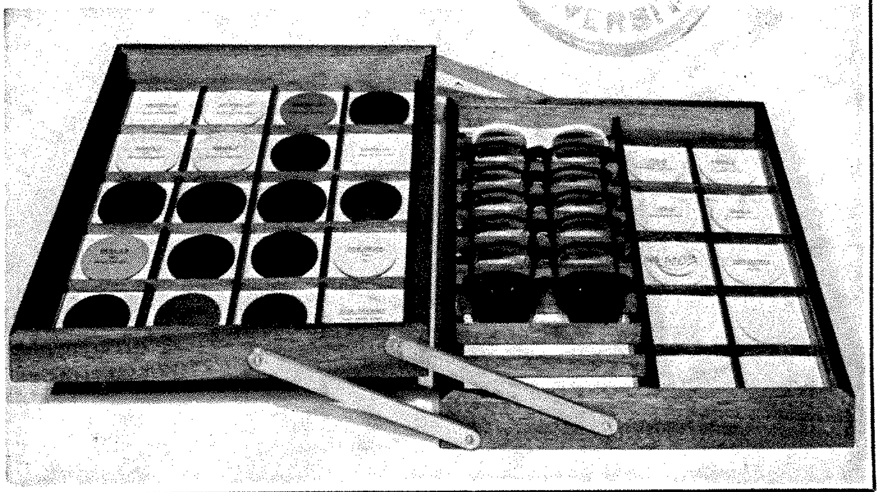

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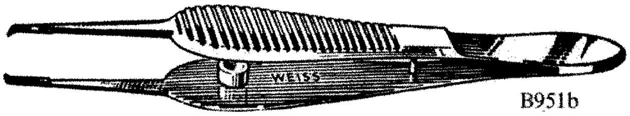

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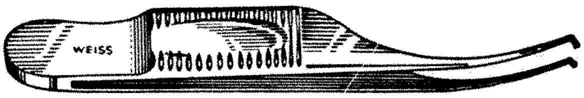

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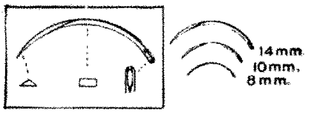

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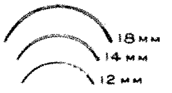

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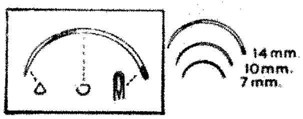

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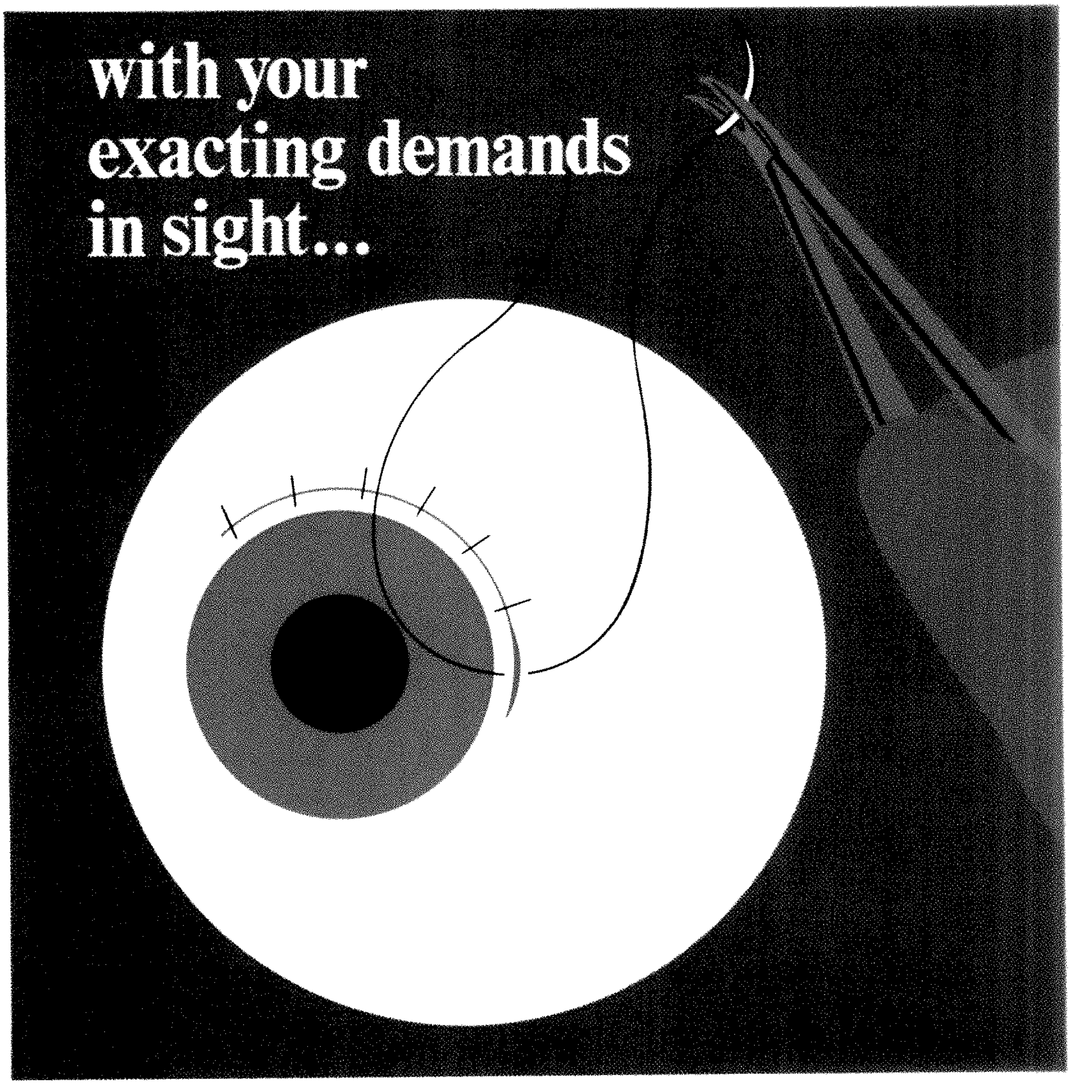

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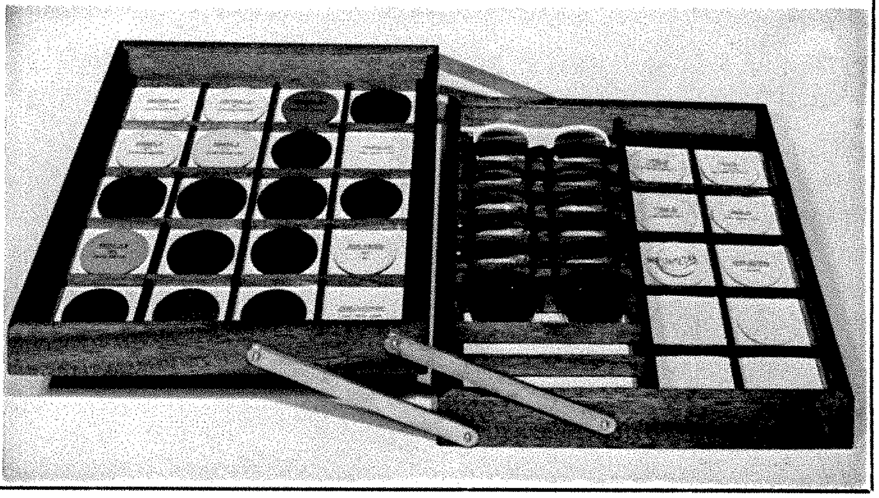

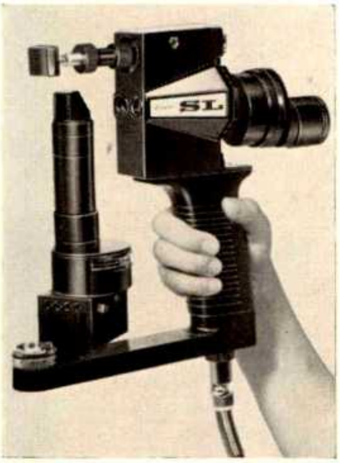

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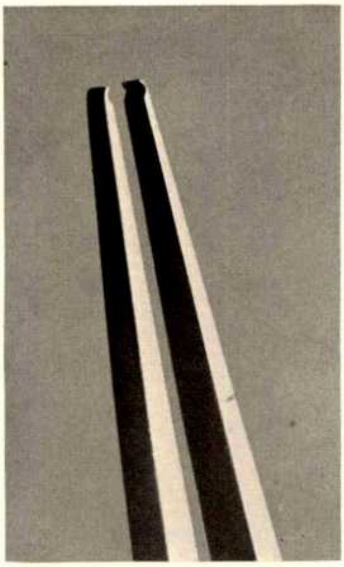

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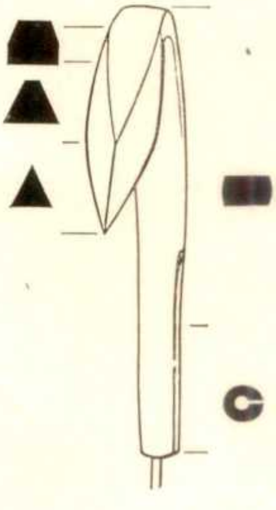

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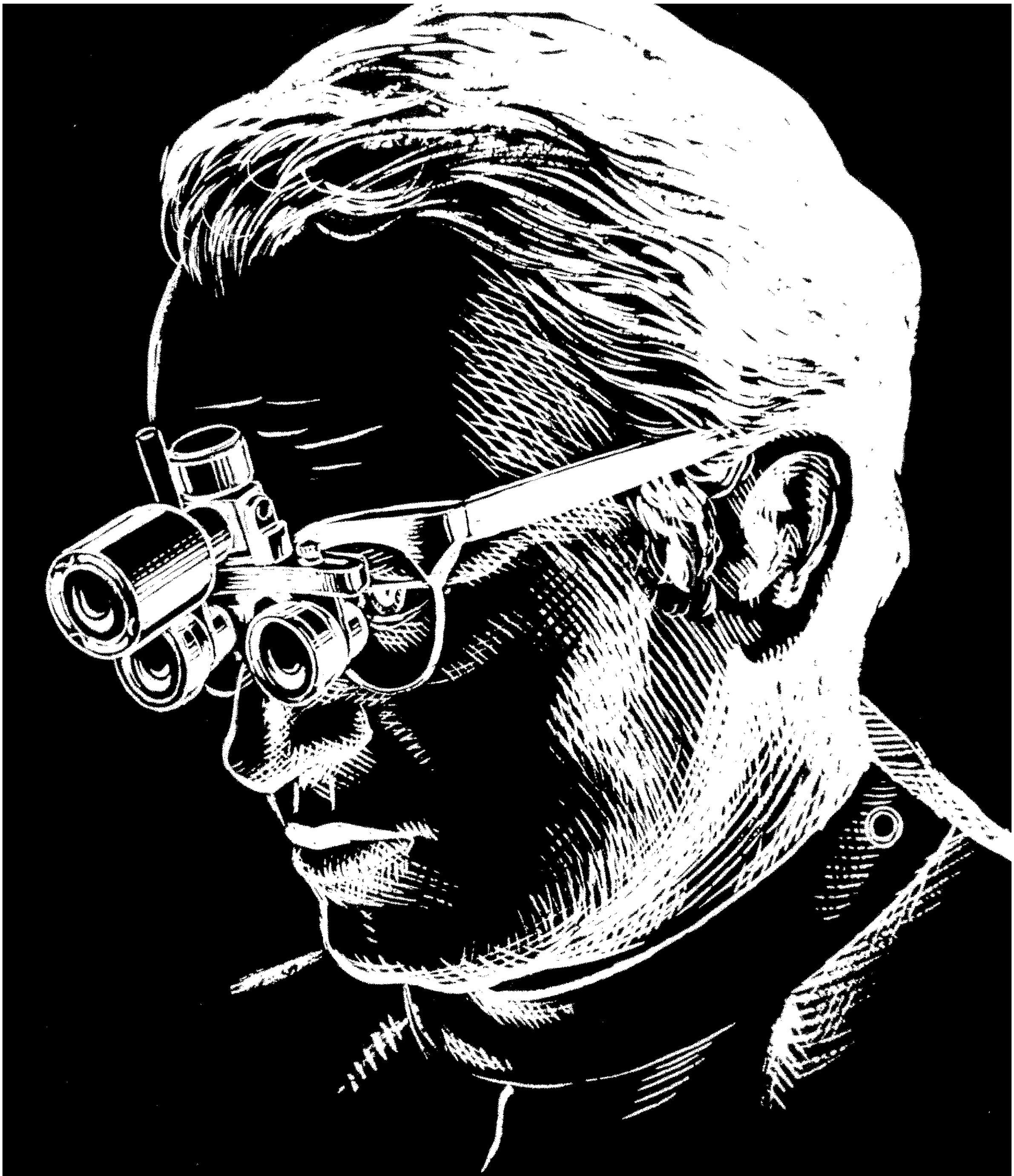

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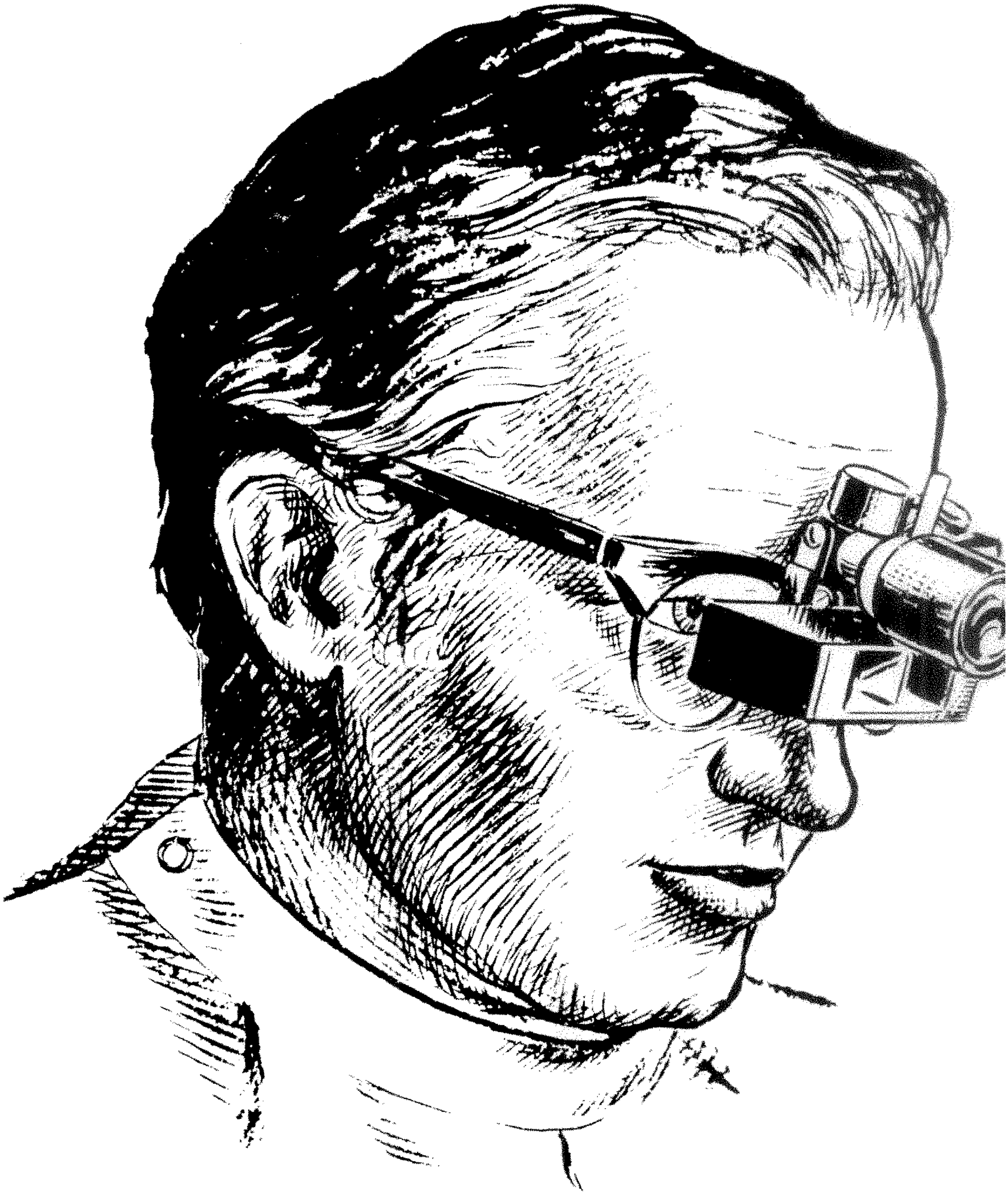

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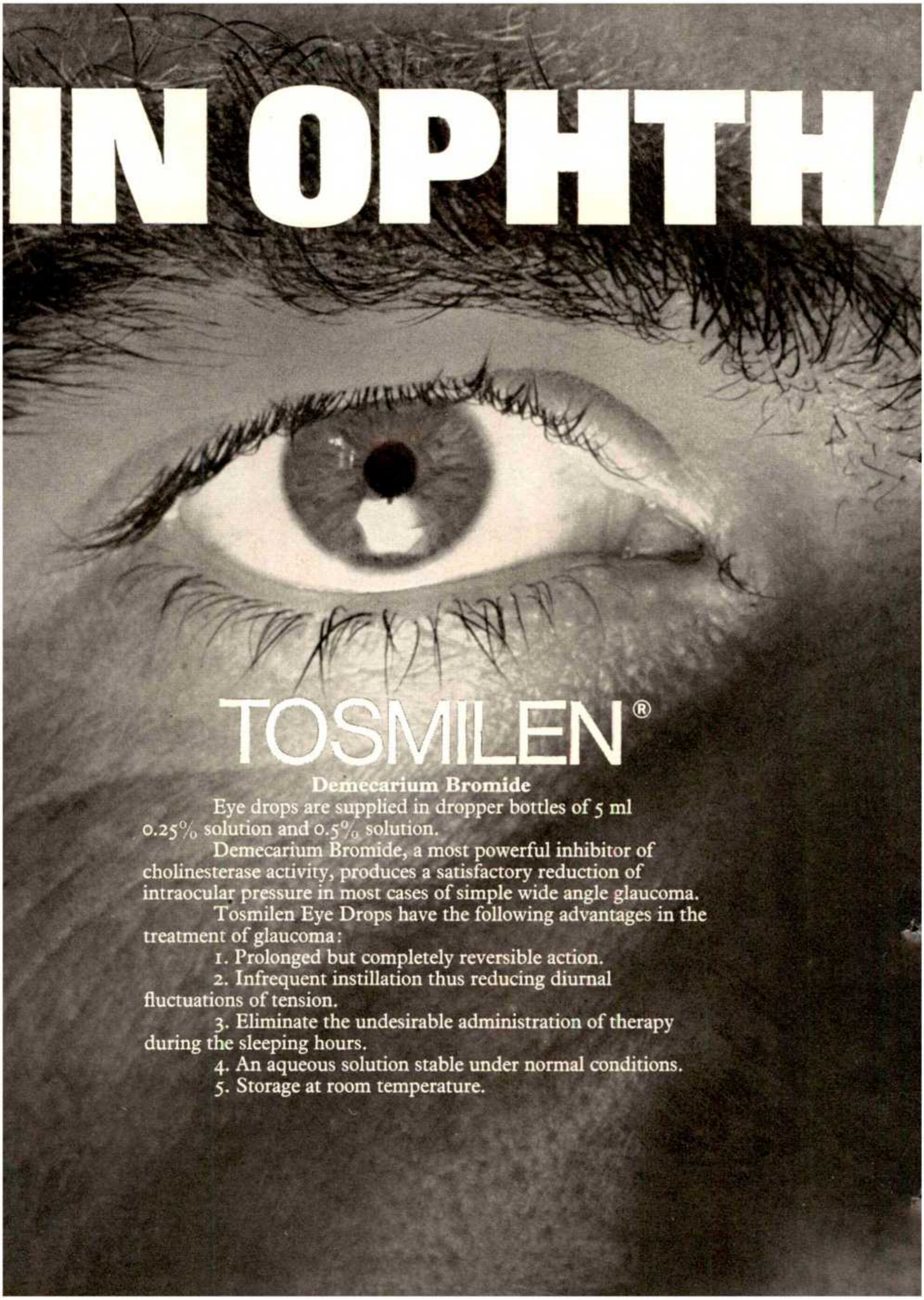

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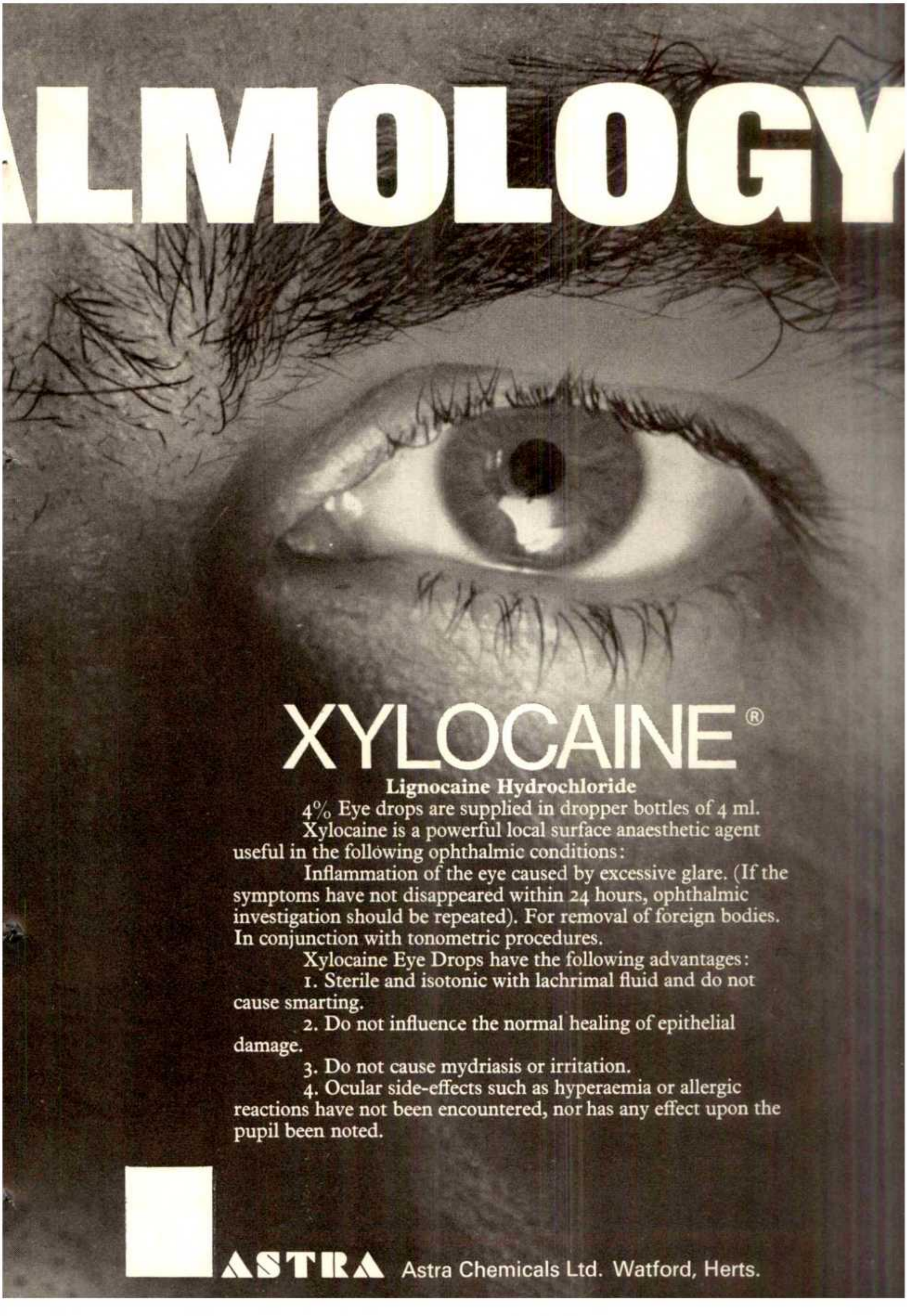

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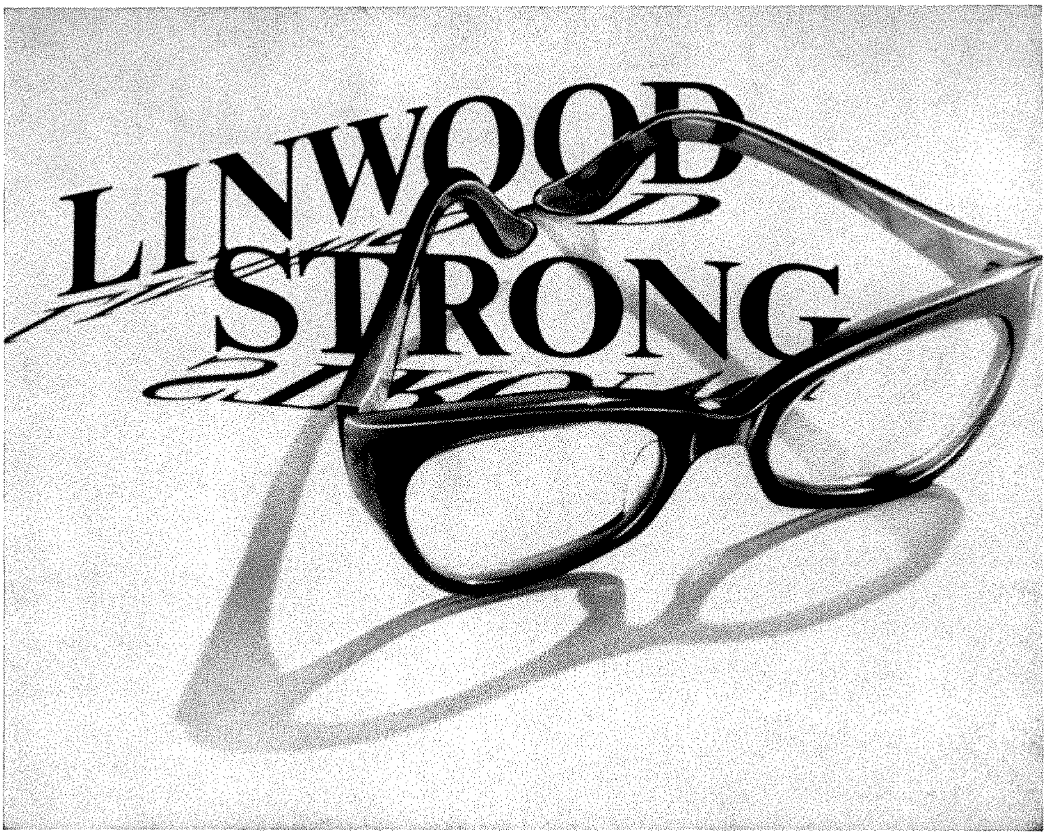

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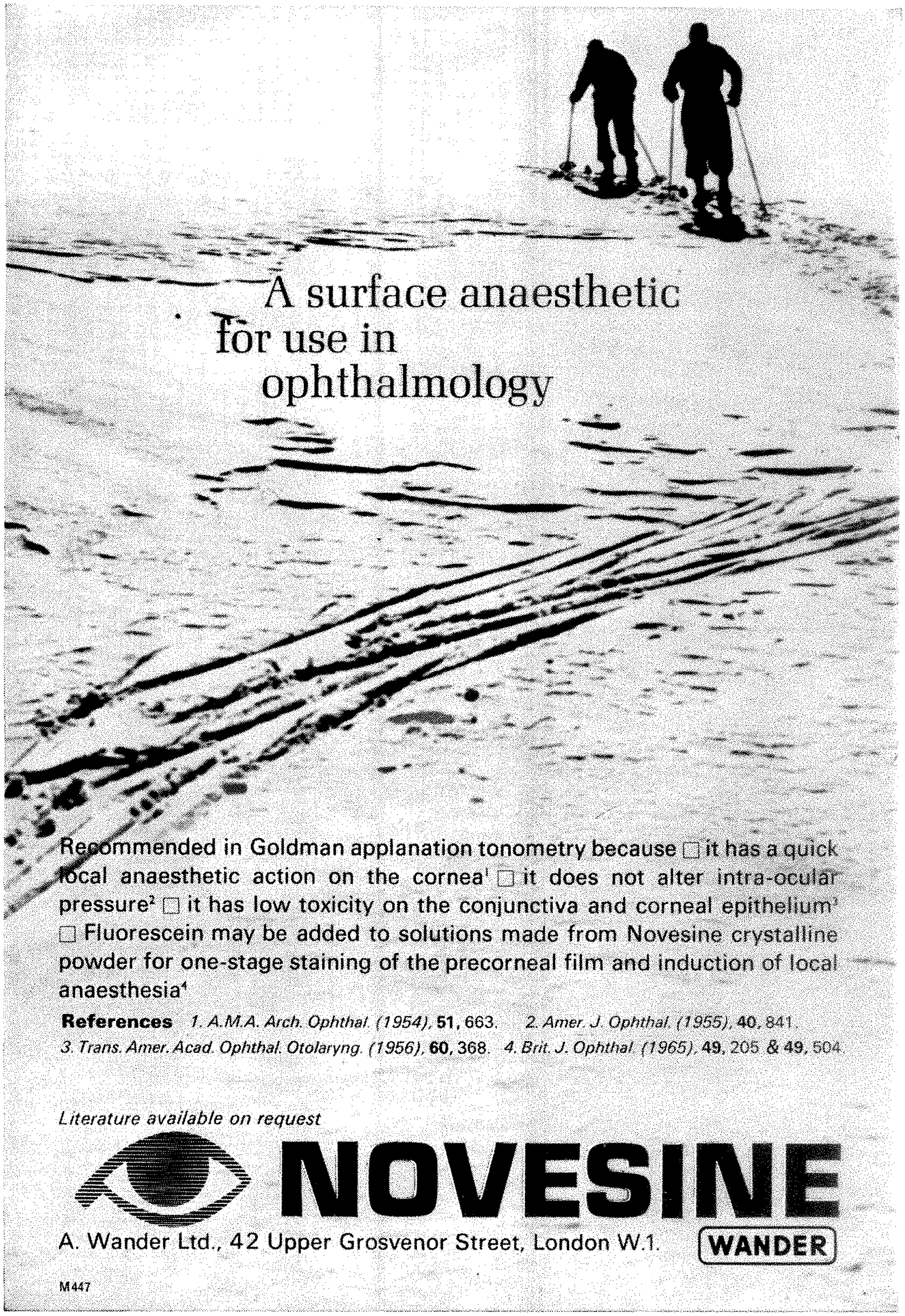

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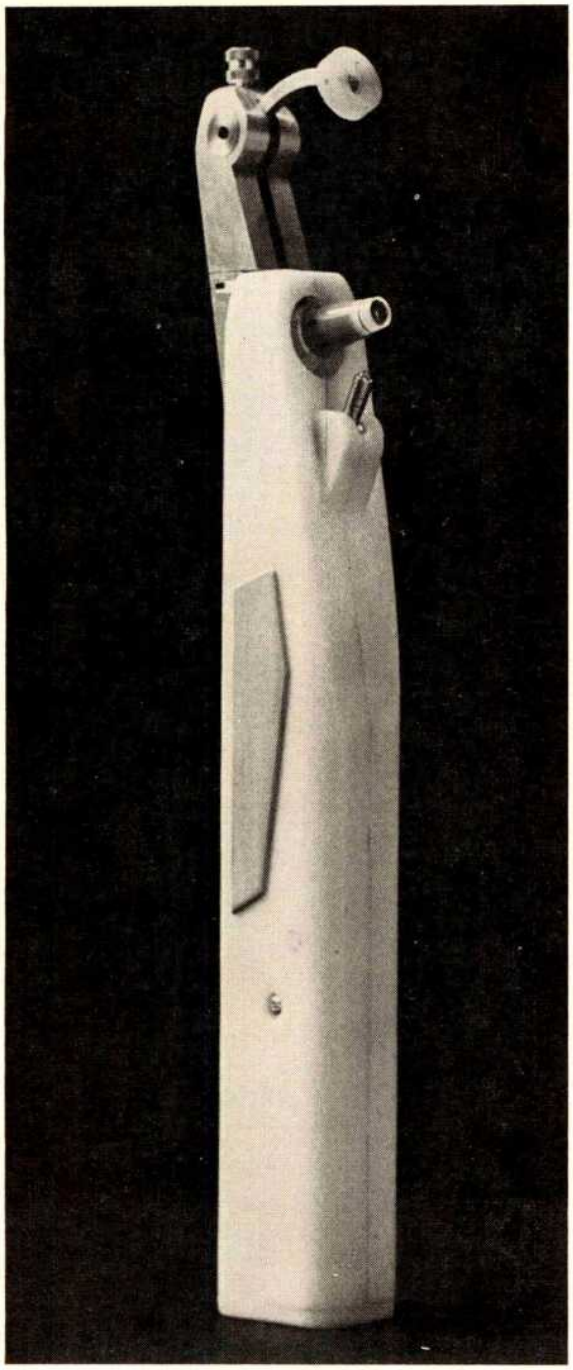

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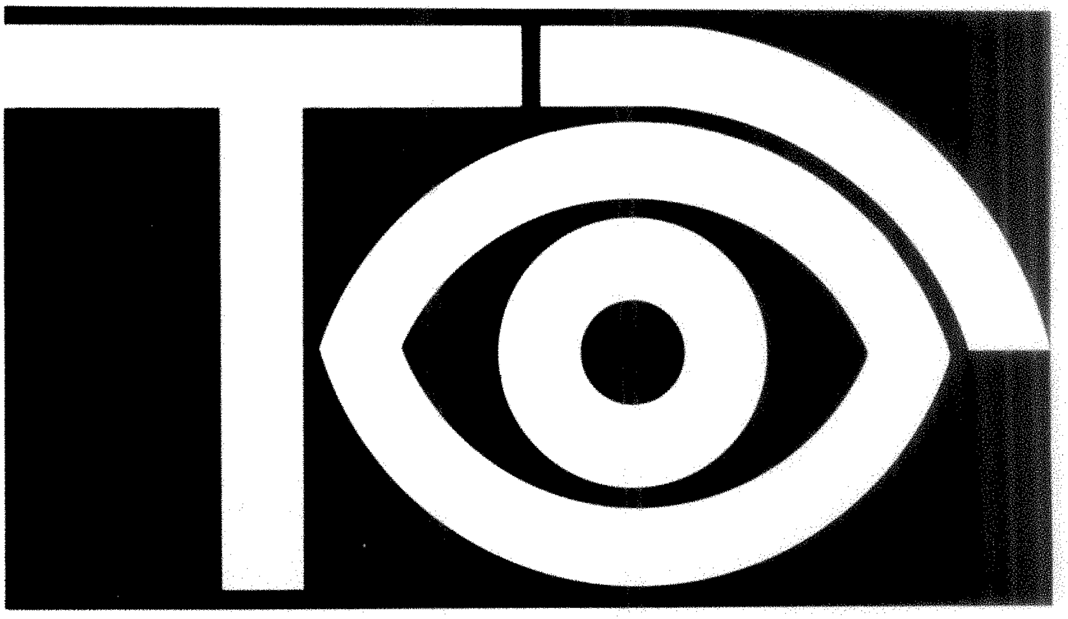

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Communications

Ocular and nervous system involvement in angioma serpiginosum

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K. V. SANDERSON

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Cutaneous angiomata of the "port wine" variety are frequently associated with angiomata elsewhere in the body and particularly in the central nervous system. Retinal and nervous system involvement by angioma serpiginosum has, however, not previously been recorded. For this reason and also because of the unusual retinal abnormality in this patient, it is felt justifiable to report this single case, which may represent a new syndrome.

Case report

A woman, born on March 13, 1929, was first admitted to the National Hospital, in July, 1950, under the care of the late Dr. J. St C. Elkington. Her parents, four sisters, and three brothers were all alive and well and there was no family history of neurological illness or of cutaneous naevi.

History

At birth her skin was normal, but at the age of 1 year some angiomatous lesions were noted on the right leg. At 5 years these were more extensive and at the age of 7 years they were treated by cautery. At age 17 the patient underwent an appendicectomy and the right pupil was reported to be larger than the left. At the age of 21 years (1950) she suddenly became aware of difficulty in elevating her right arm and over the next few months noticed clumsiness in the execution of fine movements with the right hand.

In the following years, the right arm became progressively weaker with impaired sensation in the hand and in 1962 she experienced attacks of burning pain in the upper arm lasting several hours. She also noted a sensation of fullness in the right orbit on bending down. The cutaneous angioma now involved the trunk, and new lesions appeared in the right axilla and on the adjacent medial aspect of the right arm.

In 1965 she first developed burning pain in the right side of the face, which persisted as did the attacks of pain in the right arm. The weakness of the right arm progressed and elevation became impossible without assistance. At about this time, she also began to experience attacks in which she would feel faint and occasionally fall to the ground. These episodes became more frequent, and occurred as often as four or five times a day, and though some were spontaneous others were precipitated by getting up suddenly or turning the head to the right.

In 1969, she developed nocturnal paraesthesiae in the left hand; the carpal-tunnel syndrome was diagnosed and the symptoms were relieved by surgical decompression. No change was noted in October, 1970, and she was still able to work as a hospital telephonist.

The only ocular symptom reported has been of mild deterioration of vision in the right eye.

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Examination

Detailed examination was first carried out in July, 1950, and was repeated at intervals, the last occasion being in October, 1970. Angiomatous changes involved the retina, orbit, nervous system, and the skin on the right side.

SKIN

In 1950, the skin lesions affected the right leg up to the level of the inguinal ligament; there was also a small lesion on the right forearm. New areas of involvement appeared in the next 15 years. In October, 1970, the right leg, lower abdomen, and buttock were extensively affected (Fig. 1). The right axilla, arm, cheek, and forehead showed smaller areas with less conspicuous changes.

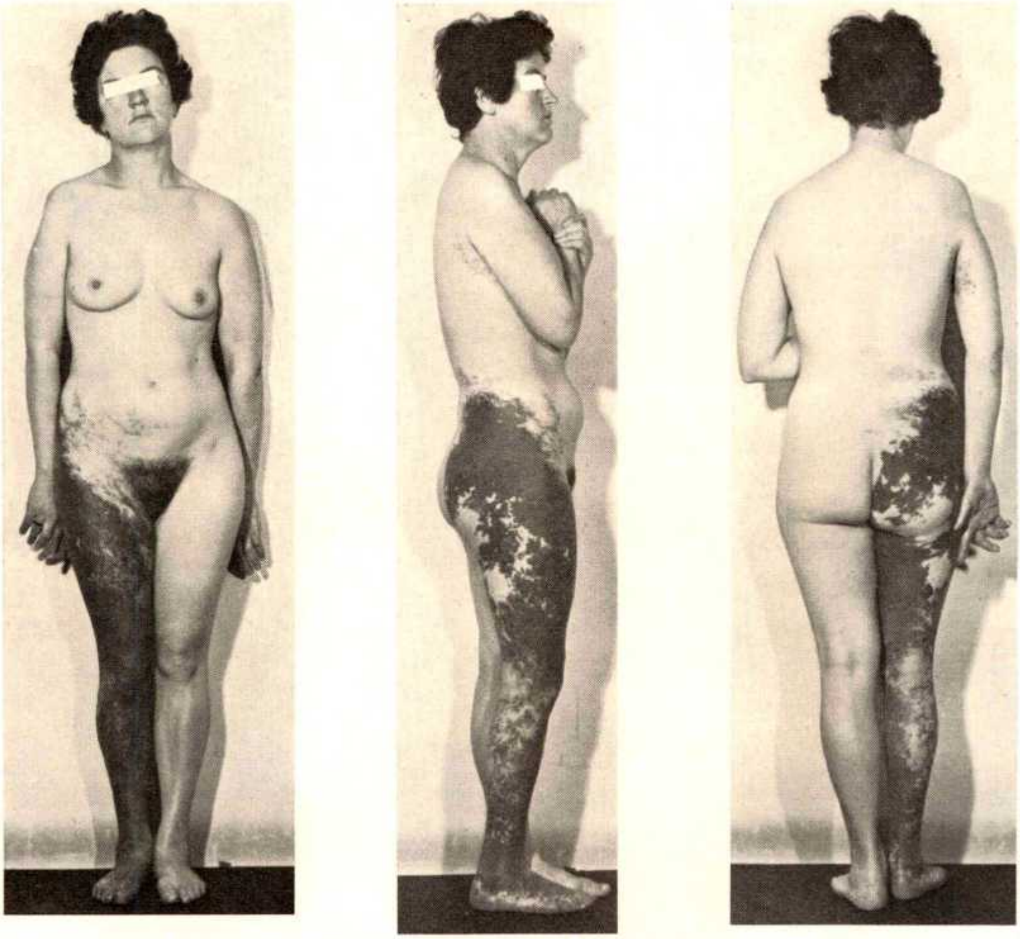


FIG. 1 *General appearance of patient in October,* 1970, *showing distribution of cutaneous lesions, and muscle wasting affecting the deltoid and forearm muscles*

The lesions in the different areas had the same basic appearance. They consisted of pinpoint to 1 mm. livid or red macules which could not be completely blanched by firm and continuous pressure (Fig. 2). The puncta were closely related, being almost confluent in the most severely affected regions. In the more recent areas, the patches were irregular and enclosed islands of normal skin (Fig. 3). In all but the mildest lesions, there was a background of erythema and fine telangiectasia which had a cyanotic hue and could be blanched by pressure. On the dorsum of the right foot,

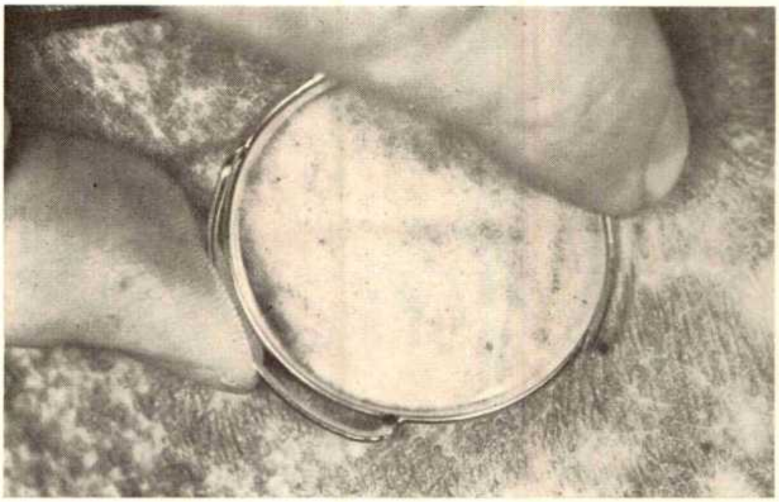


FIG. 2 *After firm pressure most of the background telangiectasia can be blanched but many puncta remain*

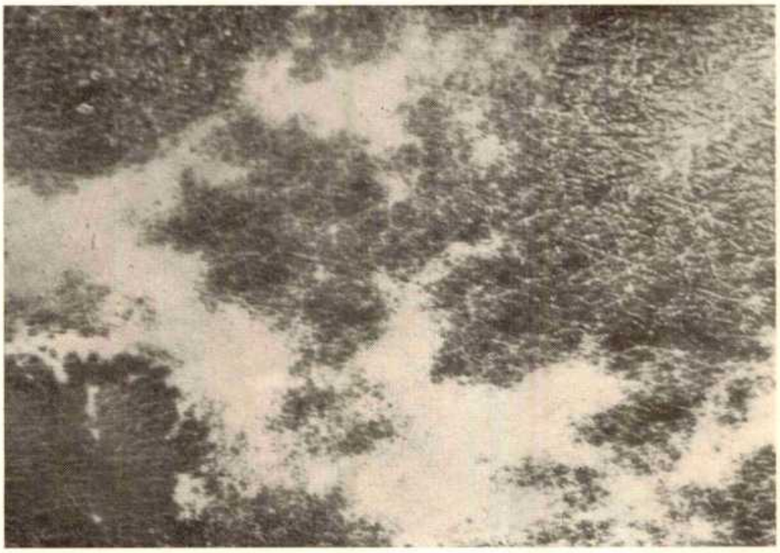


FIG. 3 *An area on the thigh, showing areas of involvement enclosing islands of normal skin*

however, the colour was bright red and in cold weather the contrast was particularly vivid. The legs were equal in size and there was no significant temperature difference, and similarly the cyanotic and bright red areas registered similar temperatures.

The skin of the thigh was biopsied in April, 1970, with one specimen from a severely affected area and the other from a less involved area. The tissue was fixed in formalin and sectioned after embedding. The most conspicuous feature of the haematoxylin and eosin preparations was the gross dilation of the capillary vessels at the tip of many of the dermal papillae. These microaneurysms distended the papillae and in places the epidermis was thinned over them (Fig. 4, overleaf). The afferent limb of the capillary loop was narrower than normal and surrounded by a thin cuff of amorphous acidophilic and periodic acid-Schiff positive material. The arteries of the dermis seemed to be poorly developed, but the venules draining affected areas were branched, tortuous, irregularly dilated, and cuffed by acidophilic material. Comparable vessels in unaffected areas were not cuffed, and microaneurysms were not seen in the tips of the papillae. Similar vascular abnormalities were seen in the connective tissue sheaths of hair follicles and eccrine sweat glands.

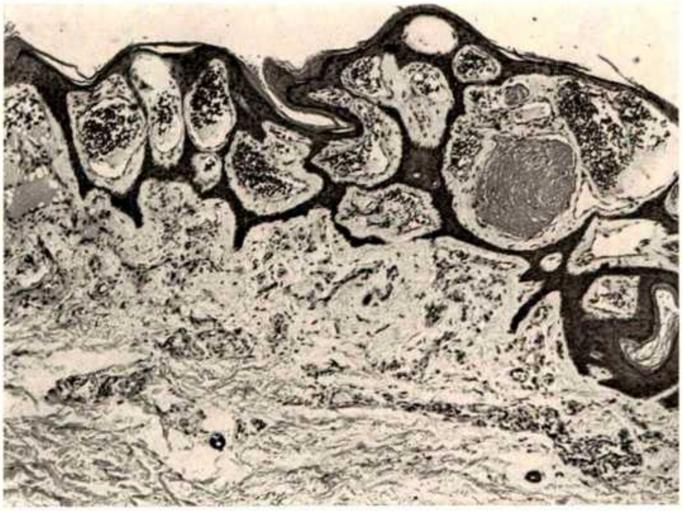


FIG. 4 *Section from the more severely affected area, showing widely dilated capillary loops, one containing a thrombus. The epidermis is stretched and raised over the expanded papillae. Haematoxylin and eosin.* × 100

When compared with the biopsy from the less severely affected area, that from the area of advanced change showed larger and more numerous microaneurysms and more severe changes in the subpapillary venous plexus. It also showed a few microaneurysms containing thrombi. With van Gieson's stain, the collagen of the papillary body was somewhat fragmented and a cleft was seen in the collagen network around some capillaries and venules. The reticulin was not altered in distribution, but the superficial elastic fibres were relatively deficient in the unaffected skin and virtually absent in the more severely affected areas.

ELECTRON MICROSCOPY

For electron microscopy small pieces of the biopsies were fixed in Millonig's 1 per cent. buffered osmium tetroxide and embedded in Epon, and thin sections were double-stained with alcoholic uranyl acetate and lead hydroxide. The sections were examined with a Zeiss EM9A microscope.

The endothelial cells of the capillaries and venules were thinned but showed no other abnormality. The subendothelial collagen bundles were infiltrated by the amorphous substance which formed lake-like accumulations in places and the normal array of the collagen fibres was disturbed (Fig. 5, opposite). The nature of the substance was not obvious nor was there any clue to its origin.

OCULAR EXAMINATION

Small telangiectatic vessels were seen on the right cheek, on the upper eyelid, and in the supra-orbital region. There was fullness of the right upper lid. No bruit was audible over the right eye or in the temporal region.

The visual acuity was 6/18 in the right eye, 6/9 with correction, and 6/5 in the left.

Near vision was N6 in the right eye and N5 in the left.

Ishihara testing showed normal responses in each eye, though the colours were brighter in the left eye. Visual field testing showed full fields in each eye to a 2/1000 white object, though qualitatively the object appeared brighter in the left eye.

Ocular movements

Abduction was full in the right eye, though all other movements were limited. Depression was most affected (40 per cent. normal), but elevation (60 per cent. normal) and adduction (80 per cent. normal) were also limited. Torsion on attempted depression was limited but present.

Pupils

The right pupil measured 7 mm. and the left 4·5 mm. and there were absent light and near responses

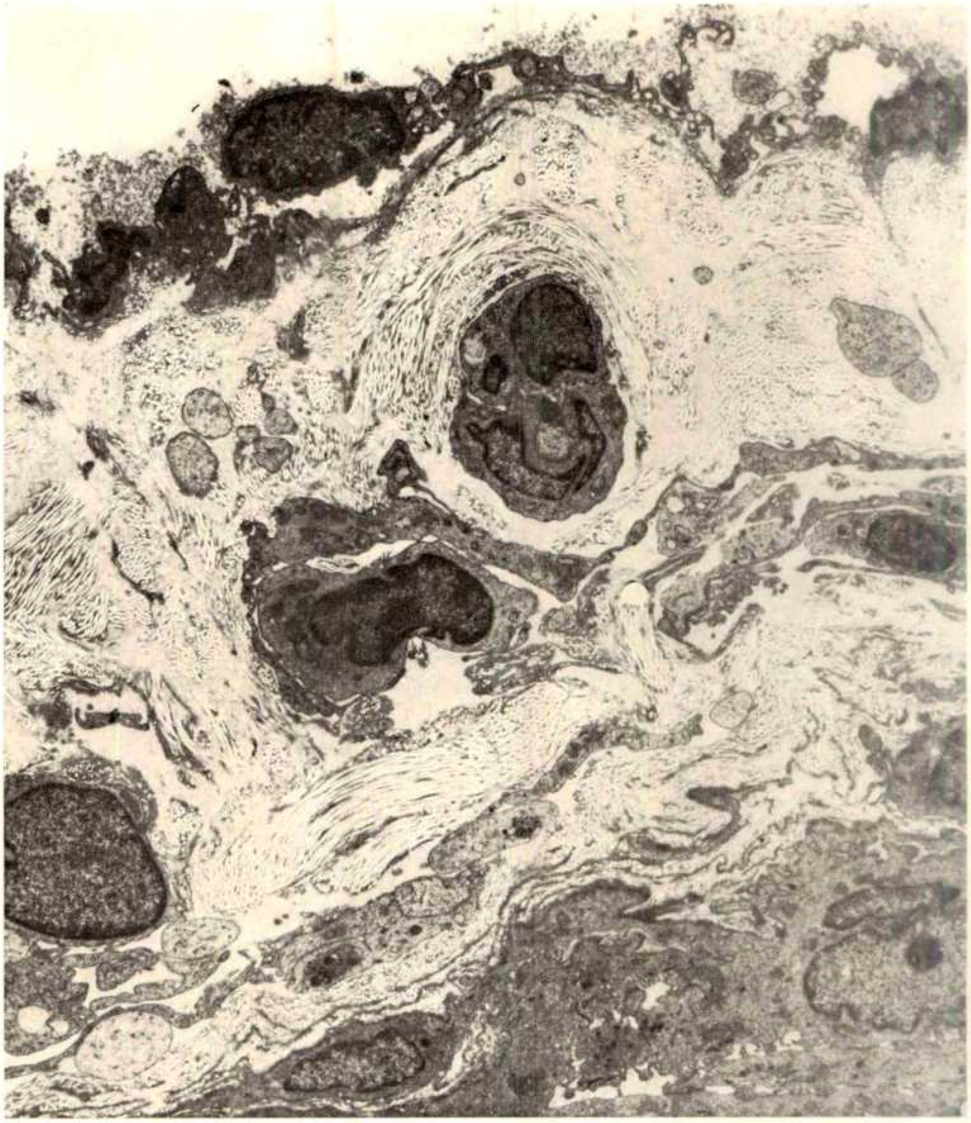


FIG. 5 *Electronmicrograph of venule wall. The endothelial cells on the right are rather flattened. The normal arrangement of the subendothelial collagen is disturbed by an amorphous infiltrate.* ×3,250

on the right. Repeated instillation of Mecholyl (2·5 per cent.) produced no pupillary constriction.

Slit-lamp examination showed no abnormality of the cornea, anterior chamber, or lens, and the intraocular tension was normal on both sides.

Fundus

The left eye was normal. The right disc was normal, but in the temporal equatorial region there was an area of diffuse capillary angiomatosis, characterized by numerous discrete capillary angiomata situated mainly at the venous end of the vascular system (Fig. 6, overleaf). Examination in 1970 revealed further angiomatous involvement related to all the other major retinal veins in the periphery.

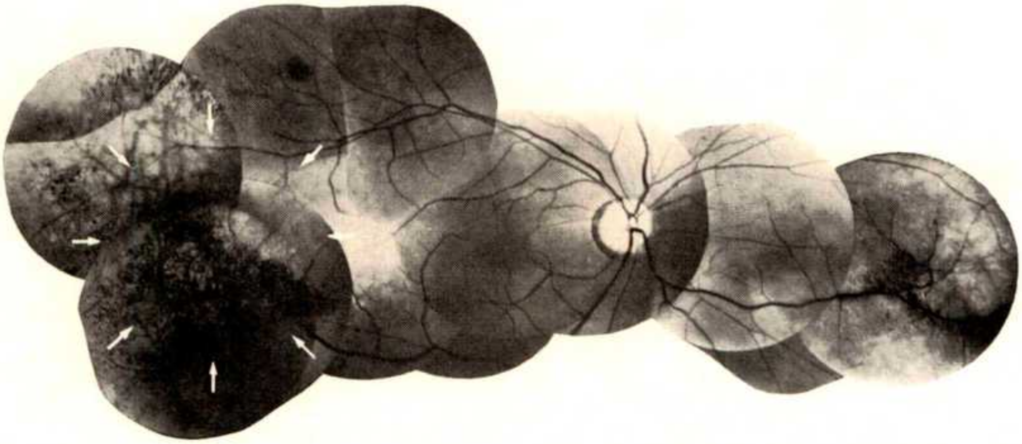


FIG. 6 *Copy of colour slides of right fundus, demonstrating angiomatous involvement particularly situated in relation to the veins in the temporal and nasal regions. Arrows represent area studied by fluorescein angiography (see Fig. 7)*

Fluorescein angiography

Rapid sequence fluorescein photography was performed after the intravenous injection of 5 ml. 20 per cent. fluorescein, using the modified Zeiss fundus camera. The arterial phase (Fig. 7*a*) shows filling of the arteries in the temporal region and these appear straightened and slightly attenuated. A few capillary angiomata are visible filled with the dye. The venous phase (Fig. 7*b*) shows irregular filling of the vein and the appearance of numerous angiomata, but in a large area in relation to the vein filling is absent. The residual phase (Fig. 7c), taken 10 minutes after injection, now shows filling of the remaining angiomata which were not previously filled. The retention of dye indicates a very slow circulation and the discrete globular pattern without leakage of dye demonstrates the integrity of the blood–retina barrier.

NERVOUS SYSTEM

July, 1950

The right pupil was dilated and showed no reaction to light. There was wasting of the right deltoid, the forearm muscles, and the thenar eminence, with weakness of abduction of the right arm, flexion of the forearm, flexion and extension of the wrist, and opposition, abduction, and flexion of the thumb. The right biceps and supinator reflexes were absent, and both plantar responses were flexor. There was minimal impairment of joint position sense and two point discrimination in the right thumb.

May, 1962

The right pupil was unchanged. The right corneal reflex and cutaneous sensation in the first division of the right trigeminal nerve were now impaired. Muscle wasting had spread to involve the spinati on the right (Fig. 1) with weakness of all muscle groups in the right arm. Cutaneous sensation from C3 to C6 and position sense in the thumb, index, and middle fingers of the right hand were impaired.

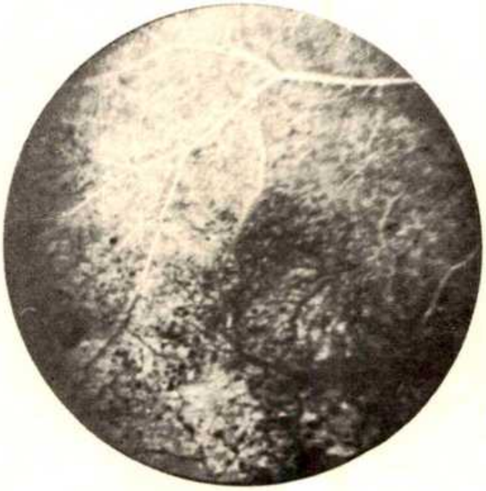
March, 1965

There was no change apart from weakness of all the external ocular muscles on the right with the exception of the lateral rectus.

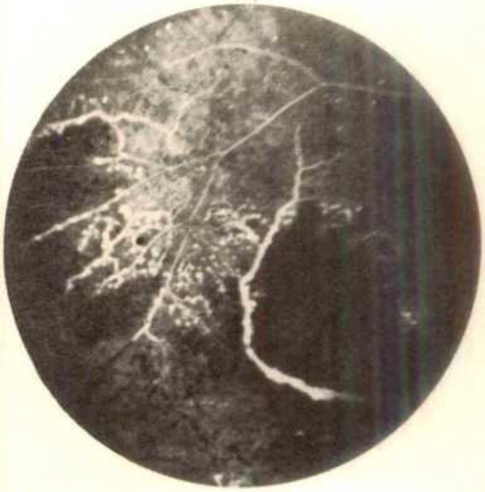
October, 1970

No further change.

(a)



(b)



(c)

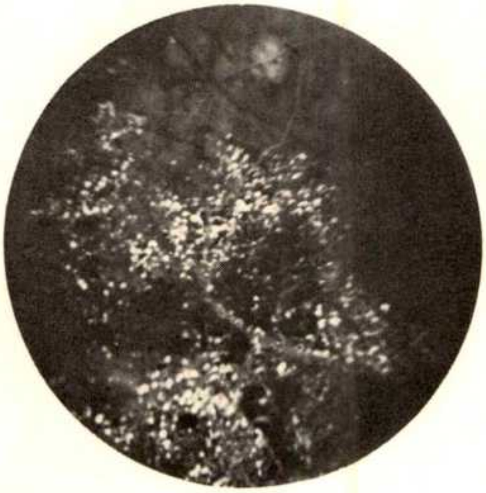


FIG. 7(*a*) *Arterial phase of fluorescein angiogram, demonstrating attenuation of arteries with early filling of some aneurysms. The venous part of the angioma is dark in contrast*

FIG. 7(*b*) *Arterio-venous phase. More aneurysms are filled and the vein is well filled, demonstrating the irregularity of its wall. A large part of the angioma within the concavity of the vein remains unfilled*

FIG. 7(*c*) *Residual phase, 5 minutes after injection. Complete filling of the majority of aneurysms has now occurred but there is no leakage of dye into the retina*

LABORATORY INVESTIGATIONS

1950 – Cervical spine *x* ray – normal
Cerebrospinal fluid – Pressure 120 mm. No cells
Protein 40 mg./100 ml. Lange – no change
Myelogram – normal
Wassermann reaction – negative

1965 – Cervical spine *x* ray – Early degenerative changes

1966 – Caloric test and audiogram – normal

1969 – Cervical spine *x* ray – Extension of spondylotic changes. Narrowing of disc space at C5–6

1970 – Caloric tests and audiogram – normal
Right carotid, vertebral, and subclavian arteriograms – normal
Electroencephalogram – normal, even during manoevures which induced attacks of dizziness
Electromyogram – evidence of chronic partial denervation in the muscles of the right arm, maximal in the deltoid, forearm flexors, and abductor pollicis brevis
Nerve conduction studies – motor conduction slower (45 m./sec.) in the forearm segment of the right median nerve, than that in the right ulnar nerve (66 m.sec.). The median nerve sensory action potential on the right was absent, while that of the ulnar was normal.

Discussion

This patient shows the classical features of angioma serpiginosum with histological confirmation. This condition, first described by Hutchinson and more recently reviewed by Frain-Bell (1957) and Barker and Sachs (1965), differs in its natural history and clinical appearance from the other vascular malformations of the skin. Females are predominantly affected with onset in early childhood, unlike the "port wine" type of telangiectatic naevus it superficially resembles, which is present at birth. The lower limb is most often involved and progression occurs until adolescence with the formation of a ringed, linear, or reticular pattern. The typical and distinctive sign is a large number of purple, red, or copper-coloured vascular puncta which cannot be completely emptied by pressure and which are not petechial. An erythematous or cyanotic background, due to engorgement of the superficial venous plexus, is a common feature and may be associated with telangiectasia. Complete or partial spontaneous cure has occurred in some cases without causing atrophy of the skin. Histological examination shows the puncta to be microaneurysms on the capillaries of the dermal papillae and of veins in the subpapillary plexus.

The patient's retinal lesions, consisting of capillary aneurysms, are remarkably similar to the changes present in the skin, but as far as the nervous system is concerned, the diagnosis is less certain. The first abnormal sign, noted at the age of 17 years, was dilation of the right pupil, which was followed nearly 20 years later by weakness of the ocular muscles supplied by the third nerve. The lesion of the third nerve was clearly separate from the extensive damage to the nerve supply of the right arm, which became apparent quite suddenly when the patient was aged 20 years and gradually progressed over the next 20 years.

The weakness and wasting of the right arm, affecting predominantly those muscles supplied by C5 and C6 and the sensory loss in the same segmental distribution, with absent biceps and supinator reflexes, suggests a lesion affecting these nerve roots. The absence of a sensory action potential from the right index finger places the lesion distal to the dorsal root ganglia. The C3, C4, C7, C8, and Tl roots were also damaged but less severely.

The patchy and lengthy distribution of the nerve root lesions and the long 20-year history with a sudden onset make the diagnosis of an angioma affecting these nerve roots or the brachial plexus, almost certain, particularly in view of the cutaneous and retinal lesions. It is probable that the third nerve disorder is due to damage to the nerve itself, as other features of a nuclear lesion are absent (Walsh and Hoyt, 1969).

Russell and Rubinstein (1963) divided the hamartomata of the blood vessels into three groups, the capillary telangiectases, the cavernous angiomata, and the venous and arteriovenous malformations. They considered the haemangioblastomata to be a separate group with neoplastic potential. The pathology of the nerve root lesions in this case is uncertain, but it is likely to be similar to that of the cutaneous and retinal lesions and to represent a disorder of the capillaries and small veins. The normal contrast studies, including myelography and subclavian, vertebral, and carotid angiography, have ruled out any malformation affecting the larger vessels.

It has proved impossible to determine the cause of this patient's feelings of faintness and attacks of loss of consciousness. Normal blood pressure readings during these episodes have ruled out postural hypotension and electroencephalograms were normal, making epileptic phenomena unlikely, as did the failure to respond to anticonvulsants. The fact

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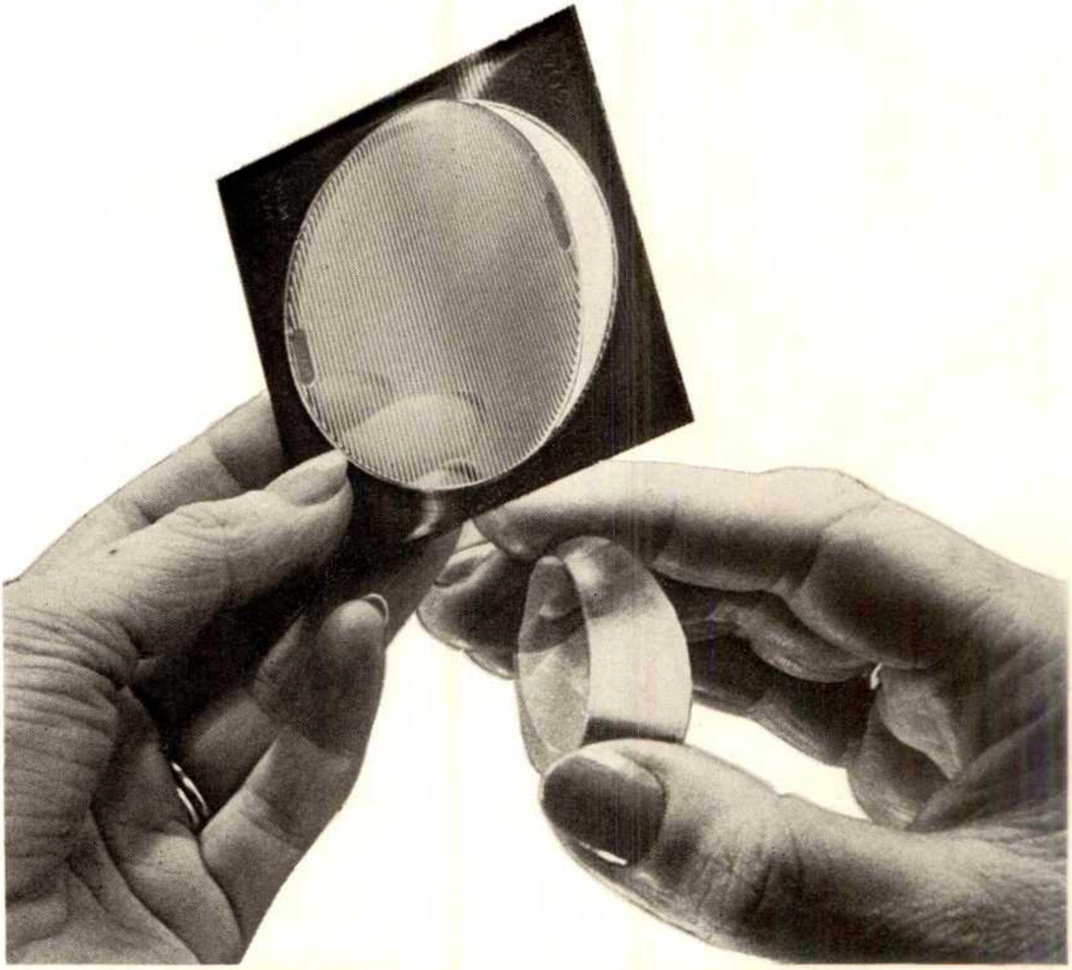

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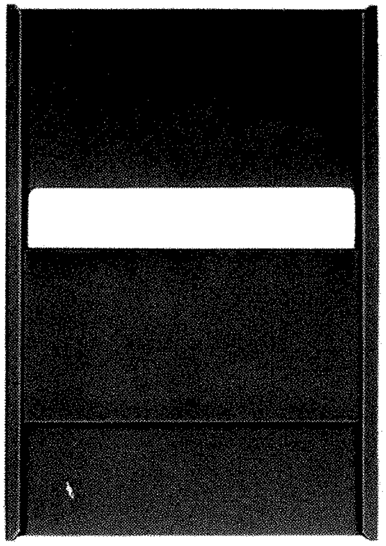

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that head-turning often precipitated these attacks raised the question of brain-stem vascular insufficiency, but both vertebral arteries and the basilar artery were normal at angiography and there was no other evidence of brain-stem dysfunction. Full neuro-otological examination failed to incriminate the vestibular apparatus. It is possible that depression and other psychological factors were playing an important part.

Many associations of vascular anomalies involving the skin, the retina, and the nervous system have previously been described:

(*a*) The von Hippel-Lindau syndrome represents the association of haemangioblastomata in the cerebellum and retina. Similar tumours may be found in the spinal cord, as well as pancreatic and renal cysts and hypernephromata. The progressive nature of the lesions which commence as capillary angioblastomata (Jesberg, Spencer, and Hoyt, 1968), the high morbidity and mortality, and the dominant inheritance of this condition place it in a separate group from the more benign angiomatoses. The retinal lesion is characterized by a progressive capillary angiomatosis with marked exudation, enormous dilation of the feeding vessels, and termination in blindness. Cutaneous naevi have been reported in this syndrome (Hall, 1934-5) but are very rare and are of the "port wine" variety.

(*b*) The Sturge-Weber syndrome is a developmental anomaly of the intracranial, ocular and cutaneous vascular systems. Angiomatosis of the leptomeninges occurs and also a "port wine". stain on the face, which may spread onto the trunk. Histopathological studies show the dilatation of the capillaries and the venules (Walsh and Hoyt, 1969). The main clinical features are related to the cerebral and ocular involvement which produce seizures and congenital glaucoma respectively. The limbs may be involved with contralateral hemiatrophy but, in some, ipsilateral hemihypertrophy may co-exist with cutaneous angiomatosis (Parkes Weber, 1929). Retinal malformations do not occur, although sheathing and tortuosity of the vessels have been recorded (Walsh and Hoyt) 1969,. Extensive choroidal involvement in the absence of retinal abnormalities has been explained embryologically by the different primordial patterns of vascular supply to the two systems (Morgan, 1963).

Closely related to this syndrome, both embryologically and clinically, is the Klippel-Trénaunay-Weber syndrome, which is characterized by the presence of naevi, congenital varices, and subcutaneous haemangiomata affecting one limb, usually the arm, in association with local hypertrophy involving the bone and soft tissues. Neurological complications are infrequent and the ocular manifestations include conjunctival telangiectases, choroidal haemangiomata, congenital glaucoma, and retinal varicosities.

(*c*) Wyburn-Mason (1943a) described a number of cases showing arterio-venous aneurysms of the mid-brain and retina, facial naevi, and mental changes. He cited one case in which cutaneous naevi were present on the trunk and on the back of the leg.

(*d*) Hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber syndrome) also represents an abnormality of the primordial vascular channels involving only the vessels of smaller calibre. Telangiectases composed of dilated arterioles and capillaries may occur in the skin, mucous membranes, conjunctiva, and retina, and also in the meninges and pia mater of the brain and spinal cord. Malformations in all these sites have a propensity to haemorrhage (Walsh and Hoyt, 1969).

The present case is different from all these syndromes in a number of respects:

(1) Angioma serpiginosum is a dermatological syndrome which is specific and quite different from the other cutaneous angiomata.

(2) The retinal lesions in this case are unusual and do not conform on clinical or fluorescein studies to those described in Leber's miliary aneurysms (Wegener, 1969). They more closely resemble the retinal telangiectasia described with hypogammaglobulinaemia (Frenkel and Russe, 1967), although in our patient the serum globulins were normal.

The particular features in our case include:

(*i*) Aneurysmal dilatation involving the retinal arterioles, capillaries, and venules.

(*ii*) Progressive spread of the lesions without enlargement of the existing ones.

(*iii*) Preservation of the blood-retina barrier, as shown by fluorescein angiography.

(*iv*) Attenuation and not hypertrophy of the feeding vessels, with areas of reduced perfusion and the development of 'shunt' vessels.

(*v*) Similarity of the retinal and cutaneous lesions.

(3) Wyburn-Mason (1943a), in his review of the literature, pointed out that, when retinal arterio-venous aneurysms were associated with similar lesions in the central nervous system, the lesions had all been situated in the mid-brain in those cases in which an adequate neurological examination had been carried out. In the present case, the major anomaly lay unquestionably in the cervical nerve roots and in the third cranial nerve.

Spinal cord angiomata are sometimes associated with cutaneous naevi, which may or may not occupy the corresponding segmental areas on the skin (Wyburn-Mason, 1943b). It is, however, uncommon to find such an extensive cutaneous lesion in a different segmental area, as demonstrated in our case.

The normal pattern of the superficial vessels of the skin is moulded by a variety of influences, including changes in blood flow and viscosity, and the effects of external stimuli and of adjacent tissues, as well as the innate potentialities of endothelial cells (Ryan, 1970). The essential pattern is laid down by the third post-natal month (Perera, Kurban, and Ryan, 1970). The course and appearance of angioma serpiginosum suggest that the basic fault is a weakness of the perithelial supporting tissue due to a local defect which has an asymmetrical and mosaic distribution and is gradually revealed by the hydrodynamic stresses within the small vessels in these areas. The precise nature of the defect is not obvious from the abnormalities seen by optical and electron microscopy. A defect in the mesodermal vasoformative tissues would therefore be the most likely explanation for the abnormalities in this case. The similar pattern of progression of the cutaneous, retinal, and nervous system lesions suggests that the vascular defect is the same in the three sites.

Summary

A case of angioma serpiginosum, complicated by capillary anomalies in the retina and spinal nerve roots, is reported.

The difference between this syndrome and the various conditions in which cutaneous, retinal, and central nervous angiomata have been described, are discussed; it is considered that this may represent a new syndrome.

It is concluded that this case provides evidence to support the view that angioma serpiginosum is due to a congenital defect of the mesodermal vasoformative tissues.

We should like to thank Mr. Prentice and the Department of Medical Illustration of the National Hospital and Miss K. Phillips of the Department of Neuro-ophthalmology for the Illustrations. We are indebted to Miss Josephine Lace for secretarial assistance.

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Haemorrhagic glaucoma

Comparative study in diabetic and nondiabetic patients

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Haemorrhagic glaucoma occurs in patients with many different basic diseases. It is most common in diabetics and in patients with thrombosis of the central retinal vein, but may also be seen in those patients with 'pure' arterial occlusions without visible concomitant affection of the retinal veins.

Most authors have described haemorrhagic glaucoma after one of these disorders, but only few have recorded comparative examinations.

A comparative study of haemorrhagic glaucoma in diabetic and non-diabetic patients seen in the Department of Ophthalmology, Aarhus Kommunehospital, during the period 1963–1968 is reported below. All patients admitted to the department for haemorrhagic glaucoma in the 5-year period are included in the study.

Material

The series consists of seventy patients with haemorrhagic glaucoma, most of whom were examined by the author.

Thirty suffered from diabetes mellitus, and the other forty were nondiabetics. In 26 of the nondiabetics thrombosis of the central retinal vein was observed either in the department or by the referring ophthalmologist. Three patients without diabetes had severe arteriosclerosis or sequelae of previous arterial embolism, but no signs of thrombosis of the central vein; in eleven the fundus could not be inspected because of opacities in the refracting media.

In the great majority of the patients retinal arteriosclerosis was observed in one or both eyes.

The age distribution of the diabetic and nondiabetic patients is given in the Table (opposite). The average ages of the two groups were 49·2 and 66·9 years respectively. This difference is statistically significant ($P < 0{\cdot}001$).

There were slightly more women than men in the diabetic group, and a definite male preponderance among the nondiabetics.

Findings

Complicating diseases affecting general health

Vascular complications were fairly common among the diabetics, symptoms from the brain, heart, or lower extremities being present in nine. Similar symptoms were seen in five of the nondiabetics. In both groups, a systolic blood pressure exceeding 150 mm.Hg was recorded in more than half the patients, and a severe blood pressure increase (diastolic

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Table *Age and sex distribution of seventy patients with haemorrhagic glaucoma*

Series		*Diabetics*	*Nondiabetics*
Age (yrs)	–29	5	3
	30–39	6	1
	40–49	3	1
	50–59	8	1
	60–69	5	10
	70–79	3	20
	80–89	–	4
	Total	30	40
	Average	49·2 ± 2·3	66·9 ± 2·6
Sex	Male	12	29
	Female	18	11
	Total	30	40

pressure exceeding 100 mm.Hg) was observed in 13 per cent. of the diabetics and 15 per cent. of the nondiabetics. Proteinuria was present in seventeen of the diabetics, but only in one patient without diabetes.

Diabetic group

Of the thirty diabetics, 29 were long-term diabetics, and 24 had proliferative retinopathy in one or both eyes. Serum creatinine was studied in 24 diabetics and in four the levels exceeded 1·5 mg. per cent.

Central vein thrombosis was observed in six of the diabetics, including four with proliferative retinopathy. The appearance of the central vein thrombosis in these six diabetics did not differ from that seen in the 26 nondiabetic patients.

Ocular changes

The haemorrhagic glaucoma showed the same clinical picture and course in both diabetics and nondiabetics.

During the period of observation bilateral haemorrhagic glaucoma occurred in six diabetics, but in only one nondiabetic with central vein thrombosis.

Intraocular pressure

In most patients in the two groups the pressure was within the range from 45 to 50 mm.Hg, but pressures about 30 mm.Hg were also recorded in both groups.

The mean values were 47·0 ± 2·2 mm.Hg (30 diabetics) and 49·6 ± 1·6 mm.Hg (40 nondiabetics).

It should be noted that there was no correlation between the level of the intraocular pressure and subjective discomfort. Some patients showed relatively low pressures and had fairly intense pain, while others had only slight discomfort although the pressure was extremely high. In some of the diabetics, who were examined at intervals of a few weeks or months, it was observed that the increase in intraocular pressure occurred gradually in step with the development of abnormal vessels on the anterior iris surface and in the chamber angle.

It is worthy of note that pain developed in two diabetics while the pressure was still very low (approx. 10 mm.Hg).

Visual acuity

Almost complete loss of vision occurred in nearly all the eyes with haemorrhagic glaucoma.

Only in one case was vision preserved. The patient was a woman aged 44 with bilateral haemorrhagic glaucoma after central vein thrombosis. The intraocular pressure returned to normal after operation, and on discharge she could count fingers at 1 m. with the right eye, the visual acuity of the left eye being 0·4.

Simple glaucoma

There was a distinct difference between diabetics and nondiabetics. None of the diabetics had, or had had, simple glaucoma, but it was found in 42 per cent. of the nondiabetics. In patients with proliferative diabetic retinopathy, the intraocular pressure is usually low. In nine out of twelve hypotonic eyes with intraocular pressures of 10 mm.Hg or less, in which haemorrhagic glaucoma of either sudden or more gradual onset subsequently occurred, rubeosis iridis was observed.

Rubeosis iridis

In nearly all eyes with haemorrhagic glaucoma, distinct rubeosis iridis was observed, with dilated vessels involving the entire anterior iris surface, both centrally and peripherally. The vessels were of the same appearance in the two groups.

When the patient was admitted to hospital, the pupil was usually small, but it became dilated in the course of the disease, and uveal ectropion then very often occurred.

Pigment deposits were occasionally observed on the posterior surface of the cornea, sometimes accompanied by aqueous flare. Occurrence of synechiae between the iris and lens was a frequent finding, equally common in the two groups. The depth of the chamber was normal in nearly all cases.

In eighteen eyes in sixteen patients, previously examined, rubeosis occurred before the development of haemorrhagic glaucoma. Fourteen of the patients had diabetes, one central vein thrombosis, and another arteriosclerosis. The time interval between the observation of rubeosis iridis and the occurrence of haemorrhagic glaucoma was more than 12 months in eleven of the eyes.

However, rubeosis iridis did not lead to glaucoma in all cases. *Nine diabetics* had at previous examinations revealed rubeosis iridis in eyes in which haemorrhagic glaucoma had not yet developed. In six of these eyes the rubeosis remained unchanged, for periods of from 2 to 6 years. In three eyes, rubeosis iridis was previously observed, but disappeared again. *One nondiabetic* with haemorrhagic glaucoma after central vein thrombosis had unchanged rubeosis iridis in the nonglaucomatous eye for a period of 4 years.

The patients considered here had primary rubeosis as defined by Ohrt (1967), *i.e.* rubeosis iridis occurs first and is then followed by haemorrhagic glaucoma after varying lengths of time.

In the present series, there was only one patient, a 68-year-old nondiabetic man with central vein thrombosis, who did not have rubeosis iridis when he was admitted to hospital with haemorrhagic glaucoma. The rubeosis which later occurred in this patient must be regarded as secondary. Otherwise, it is very difficult to say when a rubeosis is of the secondary type, since this requires the patient to be under observation at the time of onset of haemorrhagic glaucoma.

Gonioscopy

In the eyes WITH haemorrhagic glaucoma the following gonioscopic observations were made at the first examination in the two groups:

Observation	*Diabetics*	*Nondiabetics*
Open angle with vessels	15	15
Closed angle (with vessels on the periphery of the iris	7	8
Hyphaemia	4	3
Narrow angle	–	1
Open angle with synechiae	–	2
Could not be inspected	10	12
Total	36	41

Generally, it was not possible to find any difference in the chamber angle between diabetics and nondiabetics.

In the eyes WITHOUT haemorrhagic glaucoma, a normal open chamber angle was observed in most cases. Five diabetics had delicate vessels in the chamber angle at the first examination. In three of these, haemorrhagic glaucoma subsequently developed. Two nondiabetics with central vein thrombosis of the opposite eye had a narrow chamber angle, but the dilatation test did not reveal any increase in the intraocular pressure.

Treatment

Treatment of haemorrhagic glaucoma is an unrewarding task both in diabetics and nondiabetics. In nearly all cases, vision is lost, and the only objective of the treatment is to relieve the pain, which is often very intense. If the pain is intractable, enucleation of the eye is necessary.

In eighteen of the eyes, conservative treatment (pilocarpine, Diamox, and oral glycerine) or retrobulbar injection of alcohol resulted in subsidence of pain, so that further measures were unnecessary.

X ray irradiation, given in three cases, proved ineffective.

Primary enucleation of the eye was performed in two cases.

Fifty four eyes (24 in diabetics, thirty in nondiabetics) were subjected to some type of operation. The most common procedure was Preziosi's filtering operation with galvanocauterization (Merté, 1963). The postoperative course did not seem to differ in the two groups.

In spite of treatment, eleven eyes had to be removed. Histological examination showed the same changes in the anterior segment of the eye in diabetics and nondiabetics suffering from widely different diseases such as central vein thrombosis, arteriosclerosis without venous changes, retinal detachment, and dysplasia and melanoma of the choroid. Examples of the changes in the chamber angle are shown in Figs 1 to 3 (overleaf). Malignant melanoma was found in two of the eyes.

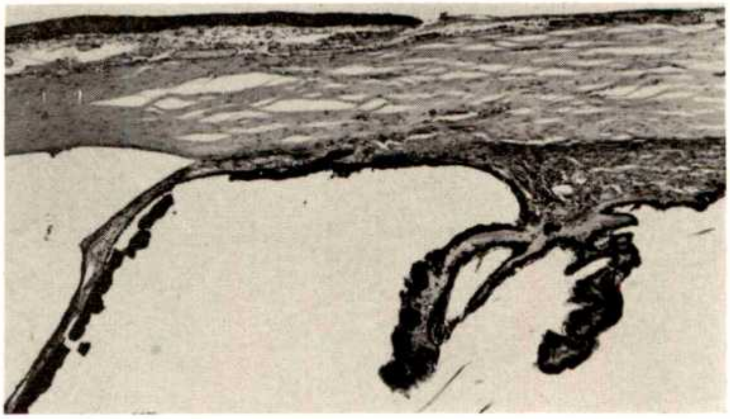

FIG. 1 *Obliterated chamber angle and atrophic iris and ciliary body in a 72-year-old man with central vein thrombosis*

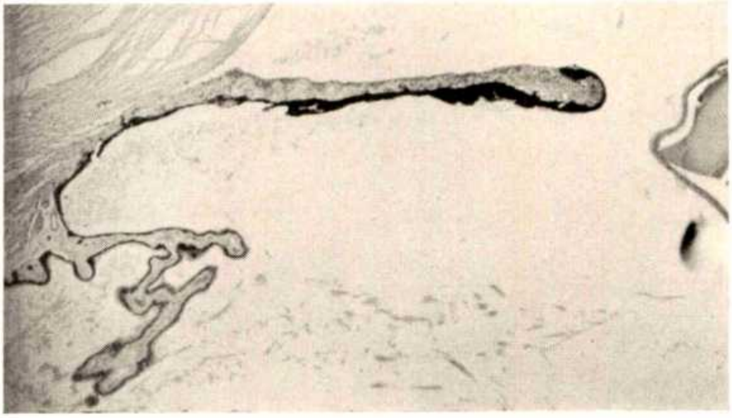

FIG. 2 *Anterior chamber in a 30-year-old woman with diabetes of 19 years duration*

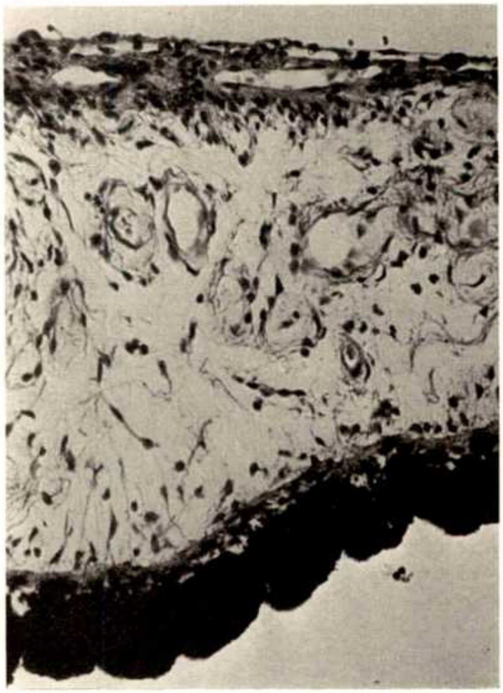

FIG. 3 *Rubeosis of the iris in a 18-year-old youth with dysplasia and detachment of the retina*

Discussion

Haemorrhagic glaucomata of identical appearance may occur in patients with widely different basic diseases. In the present study of seventy patients with haemorrhagic glaucoma admitted to an eye department during a 5-year period, there was no difference in the appearance and course of the disease in thirty diabetics and forty nondiabetics.

Special attention was paid to the changes in the anterior segment of the eye in order to disclose any possible difference between the diabetic and nondiabetic patients, but no such difference was found. Rubeosis of the iris and neovascularisation in the chamber angle are crucial features in haemorrhagic glaucoma, whether in cases of diabetes, thrombosis of the central retinal vein, or arterial occlusion. The present study showed no difference in the appearance of the vessels in the iris and chamber angle in the patients who suffered from these different diseases.

There is some difference of opinion about the type of rubeosis seen in patients with diabetes and central vein thrombosis. A few authors (François, 1955; Mylius, 1961) have distinguished between diabetic rubeosis of the iris, which was regarded as true neovascularization, as distinct from rubeosis-like vessels in central vein thrombosis which were regarded as pre-existing.

Most other authors have found no difference between the rubeosis which occurs in association with diabetes and that which follows central vein thrombosis (Sugar, 1942; Holm, 1945; Bonnet, 1949; Braendstrup, 1950; Krüger, 1961; Becker and Shaffer, 1965; Ohrt, 1967). Furthermore Wise (1956), Cucco (1961), Kadlecová (1966), and Schulze (1967) did not regard rubeosis iridis as a symptom of any specific disease, but as a sequela of a severe, long-continued vascular occlusion leading to tissue hypoxia and anoxia. Experimental occlusion of the long ciliary arteries in cats resulted in rubeosis of the iris (Schulze, 1967).

Besides the presence of rubeosis iridis and neovascularization in the chamber angle, most of the patients, both diabetics and nondiabetics, showed vascular changes in the form of retinal arteriosclerosis and, often, also venous congestion. This might support the theory that hypoxia is a causative factor in the development of rubeosis of the iris and haemorrhagic glaucoma.

Summary

A series of seventy patients with haemorrhagic glaucoma (30 diabetics and 40 nondiabetics) was studied. Among the nondiabetics, 26 had recognized thrombosis of the central retinal vein. The average ages of the diabetics and nondiabetics were 49 and 67 years, respectively. 57 per cent. of the diabetics had proteinuria, but this abnormality was present in only one nondiabetic patient.

The clinical course of the haemorrhagic glaucoma was identical in the two groups of patients. In most cases, the intraocular pressure was about 45–50 mm.Hg. Six diabetics and one patient with thrombosis of the central retinal vein had bilateral haemorrhagic glaucoma, whereas the glaucoma was unilateral in the remaining 63 patients.

Simple glaucoma did not occur among the diabetics, but was observed in about 40 per cent. of the nondiabetics.

Rubeosis iridis and vascular changes in the chamber angle were seen before or simultaneously with the onset of haemorrhagic glaucoma in 69 of the patients, whereas secondary rubeosis was encountered in only one case, *viz.* a nondiabetic patient with central vein thrombosis.

There was no difference in the clinical appearance of the anterior chamber in the patients of the two groups; it is noteworthy that the changes in the iris vessels in the diabetics as compared with those in the nondiabetic patients showed no particular characteristics.

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Macular puckers after retinal detachment surgery

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The term "macular pucker" describes the star-shaped folds and wrinkles which sometimes appear on or near the macula after surgery for retinal detachment, because of a localized area of preretinal membrane formation which contracts and causes wrinkling (Fig. 1). The density of this membrane may vary, the least dense being that seen in the condition called "cellophane maculopathy" (Maumenee, 1967) (Fig. 2). These puckers, which

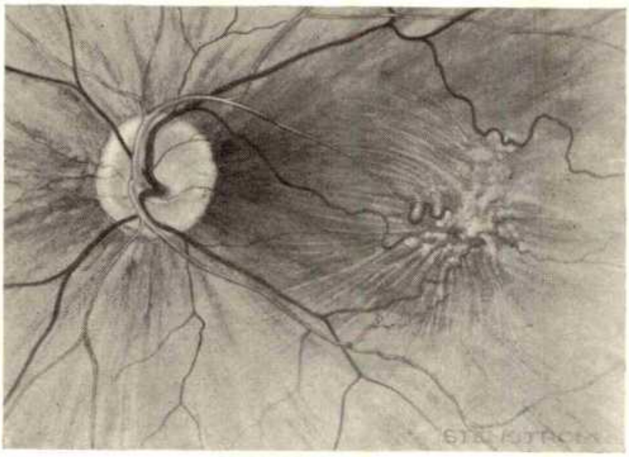

FIG. 1 *Fundus drawing of a macular pucker. Note area of preretinal organization with wrinkling of the retina, tortuosity of the vessels, and loss of the macular reflex with a greyish appearance of the macula*

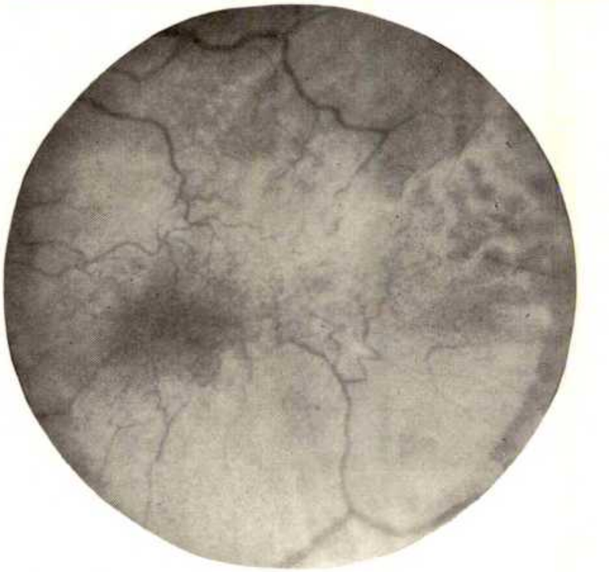

FIG. 2 *Fundus photograph of a cellophane maculopathy. Note increased tortuosity of vessels at the macula with wrinkling of the retina and loss of the macular reflex*

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have been described by Jungshaffer (1966) and Tanenbaum, Schepens, Elzeneiny, and Freeman (1970), are one of the most frequent causes of visual deterioration after successful reattachment of the retina (Sariu and Macdonald, 1970), but may also appear spontaneously in eyes which have not undergone surgery.

Spontaneous puckers may be due to pathology of the retinal periphery, *e.g.* retinal breaks, especially in the upper temporal quadrant, inflammation of the pars plana, and vitreous loss due to trauma. Idiopathic cases are rare.

In cases in which puckers occur after surgery, there is usually a gradual improvement in the sight for 2 or 3 months after a successful reattachment of the retina, but then the patient suddenly notices blurred vision, and sometimes, especially if the visual acuity is good, metamorphosia and entoptic phenomena. At this stage, the observer may see only a haziness over the macular region, but this picture quickly changes, usually within about 2 days. The vision drops precipitously and a diaphanous, greyish-white membrane may be seen overlying the macula. The edges of the membrane are sometimes seen to fuse with the posterior surface of the detached virteous. This is an alarming situation for the patient as well as for the ophthalmologist, especially if the patient had a visual acuity of 20/20 before an operation involving only the photocoagulation of a retinal tear.

It is the purpose of this paper to examine predisposing factors in the development of this condition, including the methods of reattaching the retina.

Material

In a series of 1,071 cases of retinal detachment at Emory University Hospital, 44 (16 males and 28 females) developed macular pucker. The numbers of phakic (23) and aphakic (21) eyes were almost equal. In a previous series (Hagler, Jarrett, and Presley, 1970), only 30 per cent. of cases were aphakic. The ages of the 44 patients were as follows:

Age group (yrs)	1–40	41–50	51–60	61–70	71+	*Total*
No. of cases	1	5	17	14	7	44

A similar age distribution was found by Tanenbaum and others (1970). In our previous series, 10 per cent. of retinal detachments were due to anterior dialysis and occurred in the second and third decades (Hagler and North, 1968), but none of these patients developed a macular pucker, which indicates that a young healthy vitreous is not easily affected by retinal tears.

Observations

Nine of the retinal detachments were situated on the macula and 35 away from the macula. In fifteen cases there was vitreous haemorrhage.

The lapse of time between surgery and the development of a macular pucker in our 44 cases is shown below:

Interval	*Days*			*Months*				*Total*
	1–7	8–14	15–30	1–2	3–6	7–12	12+	
No. of cases	2	2	9	16	11	2	1	44

Tanenbaum and others (1970) reported a similar lapse of time, usually 2 to 3 months. A distinction may be made between paramacular and macular puckers, because a greater degree of visual acuity may be retained with the former. Examples of the former are shown in Figs 3 to 5 and of the latter in Fig. 6.

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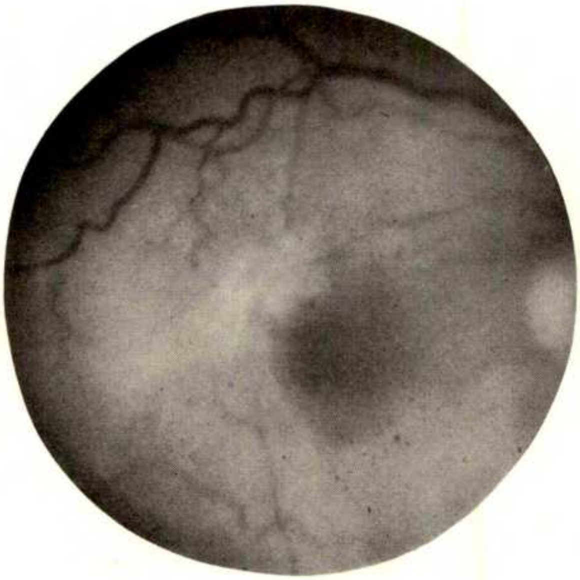

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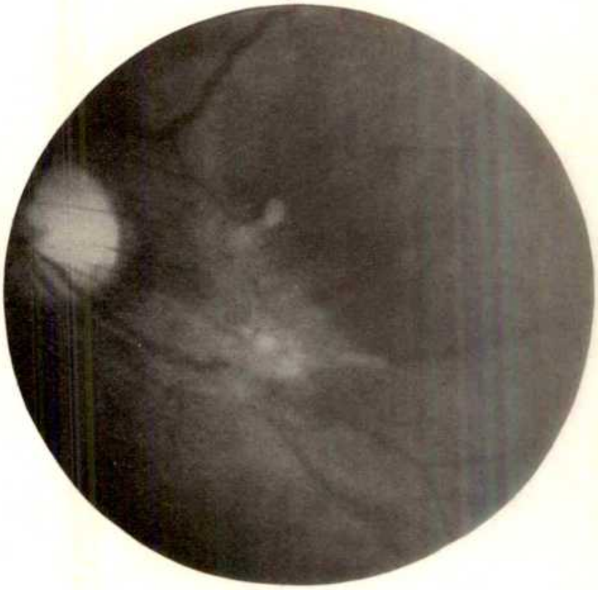

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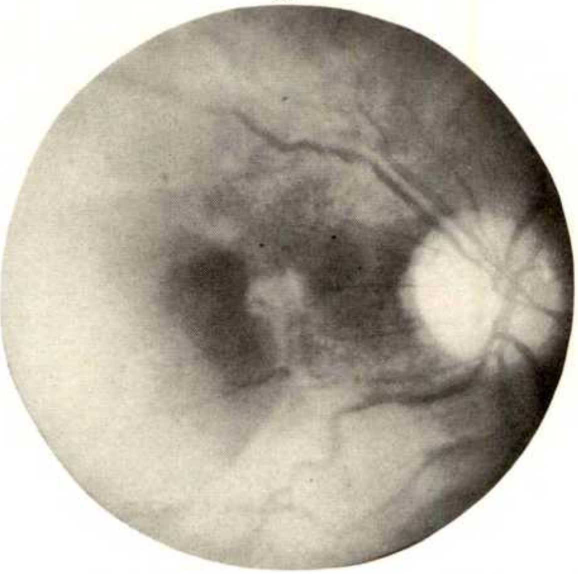

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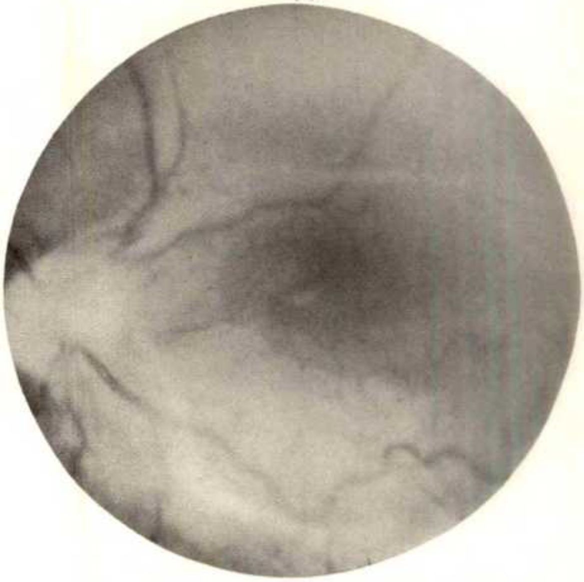

FIGS 3, 4, 5 *Fundus photographs of three cases of paramacular pucker. Note area of preretinal organization adjacent to macula.*

FIG. 6 *Very advanced stage of a macular pucker.*

Histological sections are shown in Figs 7 and 8 (overleaf).

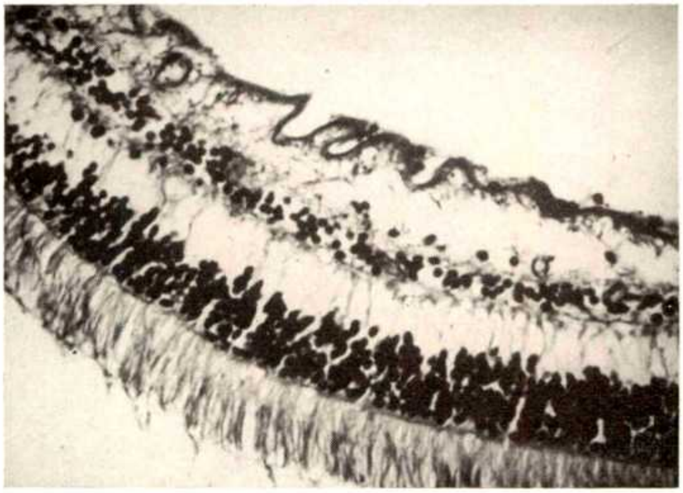

FIG. 7 *Cellular preretinal membrane causing a folding of the retina. Haematoxylin and eosin.* ×90

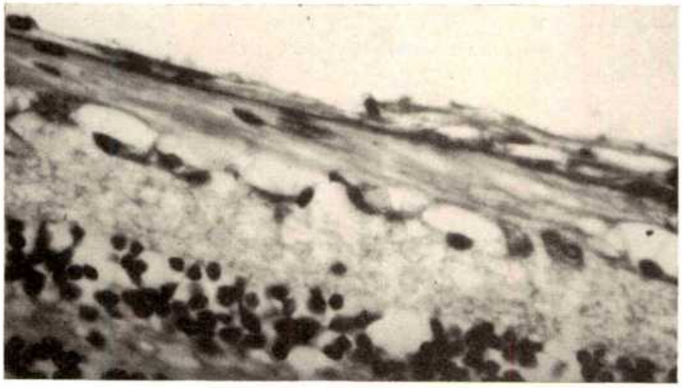

FIG. 8 *Same as Fig. 7 under higher magnification*

SURGICAL PROCEDURES (Table I)

Diathermy

The operation consisted of either a scleral buckling procedure with a silicone band followed by a diathermy, usually after a scleral resection, or a localized Custodis type procedure. The Mira radio frequency diathermy usually has an intensity setting of 40.

Table I *Development of macular puckers related to surgical procedure (percentages to nearest whole number)*

Surgical procedure	*No. of cases*	*No. with pucker*	*No. subjected to more than one surgical procedure*	*Percentage of macular puckers*	*Percentage of puckers in those having only one procedure*
Total	1071	44	14	9	6
Diathermy	322	17	4	5	4
Cryopexy	749	26	10	3	2

Cryopexy

The procedure is similar, the only difference being that we use diathermy to mark and localize the posterior edge of the tear, which is then surrounded by a single or double row of cryopexy, with either an encircling procedure or a localized external silicone implant.

Of a total of 1,071 patients, 322 (30 per cent.) had diathermy, and seventeen (5 per cent.) developed a macular pucker. In the cryopexy group of 749 patients (70 per cent.), 26 (3 per cent.) developed a macular pucker. When one considers the number of procedures used for each patient this becomes more interesting.

Of the 26 cases undergoing cryopexy, ten had had two procedures; *i.e.* sixteen patients had only one cryopexy, which reduces the number with puckers to 2 per cent.

Of the seventeen cases undergoing diathermy, four had had more than one procedure; *i.e.* thirteen patients had had only one diathermy, which reduces the number with puckers to 4 per cent. (Table II).

Table II *Comparison of preoperative and postoperative visual acuity in 44 cases*

Preoperative visual acuity	*Best recorded postoperative visual acuity*							*Total cases*
	20/15 20/30	20/40 20/50	20/60– 20/100	20/200– 20/400	*Counting fingers*	*Hand movements*	*Perception of light*	44
20/15–20/30	1	2	2	2	1	–	1	9
20/40–20/50	–		1	–	–	–	–	1
20/60–20/100	–	–		–	1	–	–	1
20/200–20/400	–	2	2	6	–	–	–	10
Counting fingers	1	–	1	2	3	–	–	7
Hand movements	–	1	–	6	3		1	11
Perception of light	–	–	–	2	2	1		5

To find the significance of these values, we used the computer to apply Fisher's Exact Test on a 2 × 2 table. The results show one-tail significance at the 0·05 level for the numerical difference between patients having one cryopexy procedure and patients having one diathermy procedure.

OUTCOME

Once a pucker is formed it does not usually progress and does not alter with further surgery. The visual improvement varies depending on whether the pucker is macular or paramacular, and it usually does not progress to *MVR*.

In our series of 44 cases (Table II), 23 per cent. improved, 23 per cent. became worse, and the remaining 54 per cent. were unchanged. This appears to be a hopeful prognosis, but unfortunately the visual acuity before operation may be as good as 20/15, as in the nine cases in the top row of the Table. The following case illustrates this possibility.

Case report

A 50-year-old white female was seen in the Emory University Clinic on November 17, 1969, with a history of flashing lights and floaters of 9 days' duration.

Examination

The visual acuity was 20/25 in the right eye and 20/20 in the left. Applanation tensions were 16 mm.Hg in the right eye and 18 mm.Hg in the left. The ocular adnexae were normal. Indirect ophthalmoscopy showed a subclinical retinal detachment in the upper nasal quadrant of the left eye (Fig. 9).

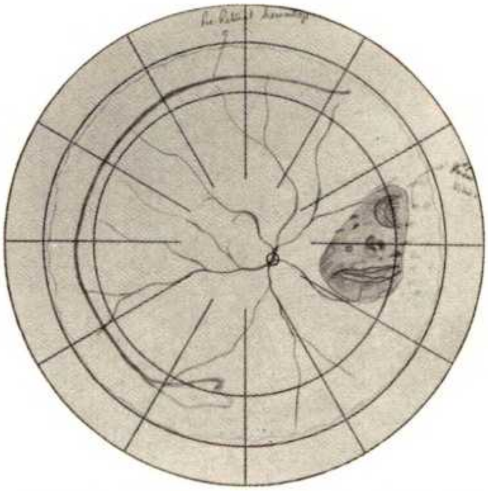

FIG. 9 *Fundus drawing, showing preoperative state of left fundus (November 17, 1969)*

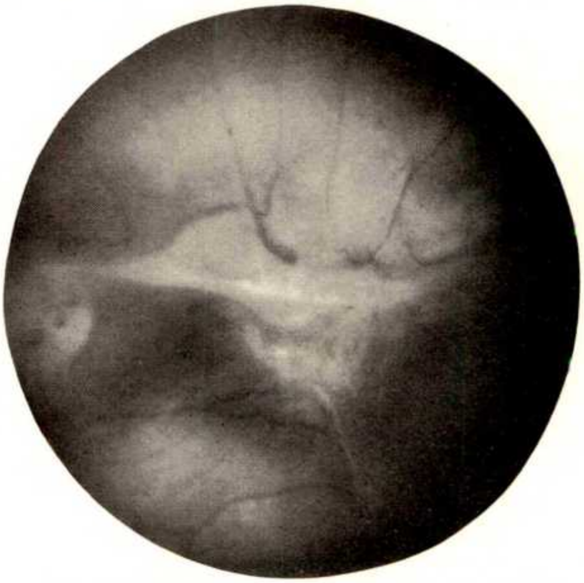

FIG. 10 *Fundus photograph. Note area of preretinal organization over the macula representing a macular pucker (December 29, 1969)*

Operation

She was admitted to Emory University Hospital on November 9, and underwent a scleral buckling procedure with an external silicone sponge implant with cryopexy of the tear and drainage of subretinal fluid at two sites, followed by paracentesis of the anterior chamber.

Result

She was examined daily with the indirect ophthalmoscope and was found to have residual fluid on the buckle which disappeared on about the 9th day. On the 11th postoperative day, since there was inadequate pigmentation of the posterior edge of the tear, she was treated with the Zeiss photocoagulator set at Green III, 4·5–0. She was discharged from the hospital 2 days later.

Follow-up

On December 15, she had 20/20 vision in the left eye, but one week later she suddenly complained of decreased vision with metamorphopsia, and on December 29 she was found to have a macular pucker (Fig. 10).

Fig. 11 (opposite) shows the progress of the visual acuity in graphic form after the development of the pucker.

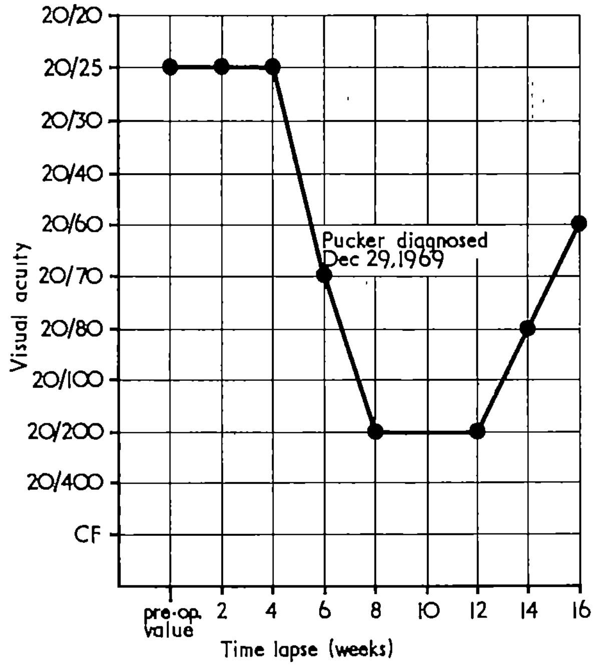

FIG. 11 *Visual results in a patient with macular pucker*

Summary

Macular pucker usually occurs in patients over the age of 50, usually between 50 and 60 years, after surgery for a retinal detachment of very short duration. Those with vitreous haemorrhage and vitreous membranes have a 25 to 30 per cent. chance of developing a pucker. In our series the type of surgery had a definite bearing on the formation of a macular pucker. Some of our patients were treated with steroids after the diagnosis of a macular pucker, but these were found to be of no value either in removing the pucker or in improving the vision.

The formation of macular puckers may be minimized in the following ways:

(1) Careful preoperative investigation to ensure that all retinal tears are discovered.

(2) The use of the least possible number of surgical procedures in reattaching the retina.

(3) The use of cryopexy rather than diathermy.

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Uveal colobomata and other anomalies in three generations of one family

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It is well recognized that typical colobomata of the uveal tract may show a strong hereditary tendency and that the transmission is usually dominant (Kelecom, 1967). Associated with such colobomata there may be other ocular anomalies, such as microcornea (Srivastava, 1961; Batra and Paul, 1967), microphthalmos (Petrovic-Ducic, 1959; Duggan and Hassard, 1961; Zeiter, 1963), aniridia (Lewallen, 1958; Menderes, 1962), medullated nerve fibres (Roy, 1965), nystagmus (Lewallen, 1958; Monahan, Hill, and Venters, 1967), heterochromia of the iris (Ammann, Klein, and Johr, 1964), persistence of primary vitreous (François, Neetens, and Carpentier, 1964), heterotopia of the macula (Bernhard, 1898), or cataract (Yanoff, Frayer, and Scheie, 1963). Only rarely, however, have systemic abnormalities been reported (Duggan and Hassard, 1961; Ammann and others, 1964; Zolog, 1966; Zaikova and Bulatovskaya, 1968). In this communication a family is presented with a high incidence of uveal colobomata in three generations, and in addition other anomalies, both ocular and systemic (Figure).

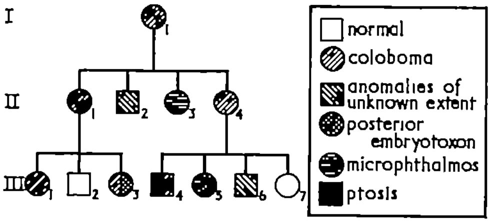

FIGURE *Family tree*

Case presentations

An infant aged 2 weeks (Patient III, 3) was referred to the Eye Clinic because of the abnormal appearance of her pupils. On questioning her mother, it was noted that this was the third generation of the family to have eye abnormalities. The pedigree was traced as far as possible and all available members of the family were examined.

Patient I, 1, a 42-year-old woman, had bilateral typical iris colobomata which extended to involve the choroid on both sides. The maculae and discs were normal and the visual acuity was 6/6 in each eye. There were localized cortical lenticular opacities bilaterally in the quadrants beneath the colobomatous areas. The appearance of the lens changes suggested that they were probably congenital in origin. No other abnormalities were present.

Patient II, 1, a 22-year-old woman, had bilateral typical iris colobomata of the bridge variety. The choroid was also involved on both sides, the lesion on the right side extending to engulf the disc and macula. The visual acuity in the right eye was hand movements and in the left 6/9. No other abnormalities were present.

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Patient II, 2, a 24-year-old man, was not available for examination as he was in a mental institution in South Africa. His mother (Patient I, 1) stated that he had iris colobomata bilaterally as well as a hare lip and cleft palate, and was severely mentally retarded.

Patient II, 3, a 20-year-old girl, was mildly mentally retarded and had gross microphthalmos on the right side. The left eye was normal with a visual acuity of 6/9. She had worn a cosmetic lens in the right socket since the age of 10 years.

When she was aged 8 months she had an operation for hare lip and one year later had her cleft palate repaired.

Patient II, 4, a 26-year-old woman, had a typical iris coloboma on the left side which extended to involve the choroid, including both the disc and macula. The right eye was normal with a visual acuity of 6/4.

Patient III, 1, an 18-month-old girl, had bilateral typical iris colobomata which also involved the choroid on both sides. The discs and maculae were normal. No other abnormalities were present.

Patient III, 3, a 2-week-old baby girl, (the propositus), had a bridge coloboma of the right iris in the usual position; this coloboma extended to involve the choroid, leaving the disc and macula undisturbed. There was a choroidal coloboma on the left side, and bilateral posterior embryotoxon Corneal diameters were normal as were intraocular pressures. She had a large cavernous haemangioma of the right breast.

Patient III, 4, a 4-year-old boy, had a moderately severe right ptosis which had resulted in the adoption of a head tilt. The right eye was otherwise normal but there was a minimal coloboma of the left choroid in the usual site, not involving the disc or macula. Facial asymmetry and a basal systolic cardiac murmur were also noted.

Patient III, 5, a 2½-year-old girl, had bilateral typical iris colobomata which extended to involve the choroid on both sides. She also has mild microphthalmos and bilateral posterior embryotoxon. In addition both pupils were ectopic, being displaced downwards and nasally. Slight horizontal nystagmus was noted. On three occasions her eyes had been examined under general anaesthesia and an intraocular pressure of up to 45 mm. Hg had been recorded in the right eye. No surgical procedure has been carried out to date, and we have no record of any detailed gonioscopic examination.

No. III, 6, a still-born boy, was an anencephalic with a hare lip and cleft palate. This information was obtained from the hospital records; no observations were made on his ocular state.

Discussion

Although the transmission of iris colobomata is usually dominant, it is often found that there is irregular penetrance with one generation sometimes being missed (Duke-Elder, 1964; Kelecom, 1967). In the pedigree reported in this communication there is almost 90 per cent. penetrance. Mello e Oliveira (1961) observed that the genes responsible for such defects were very labile resulting in a marked variation in expression. This is indeed a feature of the present series. It is interesting to note that with each generation there seems to be a tendency for the anomalies to become more gross. McKusick (1966), however, stated that this was not a true increase in the severity of the abnormalities but rather an artefactual phenomenon.

The occurrence of microphthalmos in association with uveal colobomata is not infrequent (Duggan and Hassard, 1961; Zeiter, 1963; Ernyei, 1969; Hauschild, 1969). In this family different degrees of microphthalmos are present varying from an almost totally empty socket to a slight reduction in the size of the eye. It was possible to produce a good cosmetic result in the severely affected patient by the use of a cosmetic contact lens.

The presence of posterior embryotoxon may indicate that even more widespread abnormalities of the anterior chamber may coexist, leading to a fall in aqueous outflow. The mere presence of posterior embryotoxon does not in itself lead to raised intraocular pressure (Malik, Singh, and Gupta, 1969), and it has been shown (Burian, Braley, and Allen, 1954) that 15 per cent. of normal persons exhibit this anomaly. Coscas (1969) discussed the relationship of embryotoxon to glaucoma. Even where there is no evidence of embryotoxon, abnormal tissue may occur in the filtration angle (Jerndal, 1968) leading to raised intraocular pressure. In two of the patients reported in this communication (III, 3 and 5), it was noted that posterior embryotoxon was present, and in one of these the intraocular pressure was raised. We have, however, no record available of gonioscopic examination of the angles.

The presence of ptosis is an unusual feature which has not occurred in pedigrees reported to date. As there is good levator action and a normal Bell's phenomenon, it is proposed to correct the defect surgically. This patient also has facial asymmetry, which is uncommon, though maxillary hypoplasia and mandibular dysostosis have been reported.

Abnormalities other than ocular have not often been noted, though in three of the patients in the present series there was hare lip and cleft palate. This abnormality of closure of the foetal fissures has been reported previously (Zaikova and Bulatovskaya, 1968) and in addition Duggan and Hassard (1961) recorded aural, dental, and digital anomalies. Mental dullness has been occasionally reported (Duggan and Hassard, 1961) and two of the patients in the present series were mentally subnormal, one to the extent that he needed to be cared for in an institution. Anencephaly in such a pedigree has not been recorded previously. It is unfortunate that we have no record of the ocular state of this anencephalic infant.

Patient I, 1 had localized lens opacities in both eyes in the area beneath the colobomata. Duke-Elder (1964) stated that this association of abnormalities was sometimes seen. Nixseaman (1968) had occasion to perform a lens extraction in a patient with congenital iris colobomata, and described the technique for removal of the lens *via* an inferior corneal section. In his patient senile cataractous changes were superimposed on the congenital defect.

Summary

A family is described in which ten patients in three generations had uveal colobomata with other ocular and systemic abnormalities. These anomalies are discussed with reference to the literature.

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Screening of pre-school children for ocular anomalies

I. Screening methods and their practicability at different ages

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The screening of pre-school children for ocular anomalies, particularly amblyopia has been advised by Sheridan (1960), Savitz, Reed, and Valadian (1964), Aaberg (1968), Press and Austin (1968), and Gansner (1968). However, many of the difficulties associated with screening programmes of this nature have not yet been solved. Most children under 4 years of age do not attend kindergarten or other institutions, where opportunities for group visual screening are more readily available. Furthermore, though a variety of screening tests have been suggested for small children (Sheridan, 1963; Press and Austin, 1968), there is no agreement on which best fulfils the necessary requirements.

This report represents data based on the screening of 5,329 pre-school children. The method of screening is described and the practicability of the tests used is discussed in relation to the age of the subjects.

Material and methods

The screening was performed in Beer-Sheba, a town of 70,000 inhabitants, most of whom are recent immigrants to Israel. Approximately half of the population is from North African countries (Morocco and Tunisia) and the rest are immigrants from different countries of the world. The screening period was August, 1967, to November, 1968. The children were screened in Mother and Child care clinics or kindergartens. The former are National Health Institutions providing regular antenatal care for pregnant women and medical services for children from birth to school age. The attendance at both these institutions is generally very high – approximately 90 per cent. in Mother and Child care clinics, and almost 100 per cent. in the kindergartens. This study is based on a random sample of children in these institutions.

Children

Two major groups of children were considered (Table I, opposite):

CLINICS 3,472 children aged from 1½ to 6 years, were invited for examination according to their date of birth, beginning with those born in 1965.

KINDERGARTENS 1,857 children were examined, most of whom were aged 4 to 6 years.

The screened population was subdivided into five age groups, according to age at time of screening.

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Table I *Screened population subdivided according to age at time of screening*

Population	*Total no. of cases*	*Age group (yrs)* A (1½–2)	B (2–3)	C (3–4)	D (4–5)	E (5–6)
Mother and child care clinics	3,472	472	1,438	845	497	220
Kindergartens	1,857	–	–	31	563	1263
Total	5,329	472	1,438	876	1,060	1,483

Screening tests

These were performed by orthoptists:

(1) Hirschberg corneal reflex and cover tests

(2) Visual acuity tests

(*a*) Small toys (Sheridan, 1963). The size of toys chosen correlated with a visual acuity of 6/60, 6/30, 6/21, 6/12, and 6/9.

(*b*) Matching tests, according to a modification of the method of Sheridan (1963): (*i*) Matching with numbers; (*ii*) Matching with pictures (Metallene Surgical Instruments Co.). In both these tests, the symbols were taken from conventional visual acuity charts.

(*c*) Picture charts.

(*d*) Illiterate E charts

Screening procedure

At the time of screening, every child was accompanied by one or both parents, who were asked to provide a general and ophthalmological history according to a scheduled questionnaire. Medical data was also obtained from the family records of the clinics. Thereafter, Hirschberg and cover tests were performed. The cover test for near was done in all cases and kindergarten children were also tested for distance.

Finally the visual acuity was assessed. To ascertain the degree of cooperation, the visual acuity testing began at a distance of 50 cm. with both eyes uncovered. If the child did not provide reliable answers or did not reply at all, he was considered "non-cooperative", and another visual acuity test was attempted as above. Only children who cooperated for a given visual acuity test were examined at a testable distance (3 m. at Mother and Child care clinics and 6 m. at kindergartens), using the same test.

Different visual acuity tests were used for each of the major groups:

In the Mother and Child care clinics the tests attempted included small toys, both matching tests and picture charts. Children who were examined at the beginning of this study (aged 1½ to 3 years) were examined by each of the tests mentioned above. The older groups (3 to 6 years) were tested mainly with picture charts. All these tests were performed at a distance of 3 m.

In the kindergartens a group explanation of the technique of examination was given to the class. This included a test demonstration using a child recommended by the teacher. An illiterate E chart test was performed on every child. Children who did not cooperate during this examination were subsequently examined with picture charts. Both tests were performed at a distance of 6 m. Children who did not cooperate with the illiterate E chart test or who gave unreliable answers for picture charts test at a distance of 6 m. were examined with picture charts at a distance of 3 m. Finally, if a kindergarten child did not cooperate with any of these visual acuity tests, he was referred for subsequent ophthalmological examination.

All screening and clinical data were compiled for each child on questionnaires designed for computer analysis.

Results

In this report only the results relating to the practicability of the screening tests are reported. The clinical findings will be the subject of a later report.

(1) Hirschberg and cover tests: It was possible to perform these tests on almost every child.

(2) Visual acuity tests: These were evaluated by considering the percentage of children cooperating during a given test in each age group. Since the methods used were different in Mother and Child care clinics and kindergartens, the results were reported separately and the numbers of cooperative children are summarized in Tables II and III.

Table II *Visual acuity tests in Mother and Child care clinics. Number and percentage of cooperative children with the different visual acuity tests in relation to age groups.*

Age group (yrs)	*No. of children*	*Visual acuity test*							
		Small toys		*Matching pictures*		*Matching numbers*		*Picture charts*	
		No. of cooperative children	*Per cent.*	*No. of cooperative children*	*Per cent.*	*No. of cooperative children*	*Per cent.*	*No. of cooperative children*	*Per cent.*
A 1½–2	472	29	6·1	6	1·2	2	–	25	5·3
B 2–3	1,438	122	8·4	19	1·3	2	–	193	13·4
C 3–4	845	Not performed						447	53
D 4–5	497	Not performed						406	81·7
E 5–6	220	Not performed						196	89

Table III *Visual acuity tests in kindergartens. Number and percentage of cooperative children in relation to age groups*

Age group (yrs)	*No. of children*	*Visual acuity tests*									*Total no. of cooperative children*	*Overall percentage cooperative*
		Illiterate E charts (6 m.)			*Picture charts*							
					6 m.			*3 m.*				
		No. screened	*No. co-operative*	*Percentage co-operative*	*No. screened*	*No. co-operative*	*Percentage co-operative*	*No. screened*	*No. co-operative*	*Percentage co-operative*		
C 3–4*	31	31	2	–	29	16	–	13	8	–	26	–
D 4–5	563	563	238	42·3	325	286	88	39	10	25 6	534	94 9
E 5–6	1,263	1,263	919	72·7	344	291	84·6	53	8	15·1	1,218	96·5

*This age group was too small and without statistical significance

MOTHER AND CHILD CARE CLINICS (Table II)

Children of the lowest age groups A and B were least cooperative when matching tests were used. Cooperation improved when small toys and picture charts were employed. Only 5·3 per cent. of the children in age group A cooperated with picture charts compared with 89 per cent. in age group E.

KINDERGARTENS (Table III).

The prevalence of cooperation with illiterate E charts was 42·3 per cent in age group D and 72·7 per cent. in age group E. Of the remaining "non-cooperative" children, 88 per cent. in age group D and 84·6 per cent. in age group E cooperated with picture charts at a distance of 6 m. Of the "non-cooperative" children tested with both the above tests, 25·6 per cent. in age group D and 15·1 per cent. in age group E cooperated with picture charts at a distance of 3 m. The overall percentage cooperation in children aged 4–5 years was 94·9 per cent., and in those aged 5–6 years it was 96·5 per cent. In age group C, consisting of 31 children, the prevalence of cooperation was not calculated as there was no statistical significance to such a small group of children.

In Table IV the percentages of cooperative older children (age groups D and E) of Mother and Child care clinics and kindergartens are compared. The figures for kindergarten children are related to the overall cooperation in all the visual acuity tests.

Discussion

Screening tests for the detection of amblyopia and binocular disturbances in young children should be designed to be independent of cooperation and easy to perform. With the conventional methods of examination at our disposal, no single test can fulfil these requirements, and accordingly, in the present study, every child was screened with three tests.

The Hirschberg and cover tests provided information which to a great extent was not dependent on the degree of cooperation. Since it was possible to perform both these tests with almost every child, even in the lowest age groups, they proved very valuable. Nevertheless, they do not provide adequate information on ocular anomalies unassociated with squint. In the present study different visual acuity tests were performed in an attempt to determine the best method of screening for each age group and the value of these tests was assessed in relation to their accuracy and the extent of cooperation in the different age groups.

In age groups A and B (1½–3 years), the visual acuity tests used proved to be of little value until the age of 3 years, mainly because of lack of cooperation.

In age group C (3–4 years), 53 per cent. of the children could be screened with picture charts. It is probable, however, that a high percentage of ocular disturbances still remained undetected in the "non-cooperative" children. Whether this age group is suitable for screening will be discussed in later reports, taking into account the incidence of anomalies diagnosed at this age.

In age groups D and E (4–5 years), cooperation was high. The kindergarten children were significantly more cooperative (94·9 and 96·5 per cent.) than those of corresponding age examined in the Mother and Child care clinics (81·7 and 89 per cent.) (Table IV).

Table IV *Visual acuity tests. Comparison of percentage of cooperative children in the older age groups in clinics and kindergartens.*

Age group (yrs)	*Prevalence of cooperation in mother and child care clinics*	*Prevalence of cooperation in kindergartens**
D 4–5	81·7	94·9
E 5–6	89	96·5

*The figures for kindergartens are related to the overall cooperation obtained during all the visual acuity tests

This may be related to the fact that children regard the clinics as medical institutions and are less relaxed. In the kindergartens, the test was regarded as a game and the children volunteered to be examined. Moreover the methods of testing visual acuity in the two groups were different.

The picture chart test was more understandable to the children than the illiterate E chart. However, the latter is more accurate, and a fairly high percentage of children aged 4–6 years were cooperative in performing it. It therefore seems advisable to screen the visual acuity of children of this age by the method used in the kindergartens.

The results of this survey are not in accordance with those of Press and Austin (1968). In their study the children were examined at home by their own parents using Sjögren visual acuity charts, and a higher rate of cooperation was apparently obtained in the 3–4 year old children. It is possible that the Sjögren charts are more easily understood than the illiterate E charts, although their accuracy does not exceed that of picture charts. The higher degree of cooperation is probably also related to the fact that the Press screening method was confined to a population which mainly included children of high and middle-class levels. In the present survey the population consisted mainly of children of the lower social level with a minority of middle-class children. It is also possible that the Press results were related to the fact that the tests were performed by untrained staff in a home environment

Summary

(1) A total of 5,329 pre-school children (aged 1½–6 years) were screened for ocular anomalies in two separate localities and classified in five age groups.

(2) The screening tests included: the Hirschberg corneal reflex and cover tests and visual acuity tests comprising small toys, matching tests, picture charts, and illiterate E charts.

(3) It was possible to perform the Hirschberg and cover tests with every child.

(4) Different degrees of cooperation were found in the five age groups using the visual acuity tests:

(*a*) Up to the age of 3 years only a small percentage of children cooperated in visual acuity examinations no matter what test was used.

(*b*) From 3 to 4 years 53 per cent. of children cooperated using picture charts.

(*c*) At the age of 4 to 6 years a high degree of cooperation was found (up to 96 per cent.). It is suggested that visual acuity should be examined at this age with the illiterate E charts, and that picture charts should be used with "non-cooperative" children.

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Screening of pre-school children for ocular anomalies

II. Amblyopia. Prevalence and therapeutic results at different ages

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It is generally assumed that early diagnosis and therapy improve the prognosis of amblyopia, and screening of pre-school children for this disease has therefore been advised by many authors (Savitz, Reed, and Valadian, 1964; Press and Austin, 1968; Gansner, 1968). The best age for screening has not yet been established, probably because of the diagnostic difficulties encountered in examining very young children.

This report presents data on the incidence of amblyopia in an almost unselected population of 5,329 children between the ages of 1½ and 6 years. The relation of the age at which amblyopia was diagnosed to therapeutic results was also studied in an attempt to clarify some of the problems related to the choice of the most suitable screening age for pre-school children.

Methods

A detailed description of the screened population subdivided into five age groups, the screening tests used, and the procedures have already been reported (Oliver and Nawratzki, 1971).

The diagnostic criteria for amblyopia in this study were:

(1) Unilateral tropia confirmed by the cover test;

(2) An obvious difference in the behaviour of the child when one eye was covered, as compared with the other;

(3) A difference of at least two lines between the two eyes, calculated for a distance of 6 m. on the visual acuity chart, with correction if necessary.

Whenever a visual acuity test could be performed, it was used as the basis for the diagnosis. In young children who did not cooperate during the visual acuity test, the diagnosis was established by the first or second criterion or both,.

Children in whom these tests for amblyopia were positive were referred to the Outpatient Clinic of the Ophthalmology Department of the Negev Hospital, Beer-Sheba, for further investigations. There they were examined by an ophthalmologist, an orthoptist, and an optometrist, who decided on the diagnosis and subsequent treatment. The latter included glasses, the use of a ½ per cent. solution of atropine eye drops in the healthy eye (mainly in the younger children), conventional and inverse occlusion, pleoptic treatment (in a few of the oldest children), and surgery. The follow-up examinations and therapy were performed by the same team.

Patients with evidence of organic eye disease were excluded from the study.

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Results

Among the 5,329 children examined, a total of 67 cases of amblyopia were found – 36 boys and 31 girls. The right eye was affected in 34 children and the left eye in 33.

The prevalence of amblyopia encountered in each of the five age groups (Table I) ranged from 0·4 per cent. in the youngest age group (1½ to 2 yrs) and to 2·1 per cent. and 1·6 per cent. in the oldest age groups (4 to 6 yrs).

Table I *Prevalence of amblyopia in each of five age groups*

Age group (yrs)	*A* (1½–2)	*B* (2–3)	*C* (3–4)	*D* (4–5)	*E* (5–6)	*Total no. of children*
No. of children screened	472	1438	876	1060	1483	5329
Cases of amblyopia No.	2	9	9	23	24	67
Per cent.	0·4	0·6	1·0	2·1	1·6	Mean 1·2

Table II shows the relationship of amblyopia to ocular deviation. Cases of amblyopia without squint were not found until the age of 3 years, and in the oldest age groups 38 per cent. of those with amblyopia showed no strabismus.

Table II *Relation of amblyopia to type of ocular deviation in each of five age groups (percentages in parentheses)*

Type of ocular deviation	*Age group (yrs)* *A* (1½–2)	*B* (2–3)	*C* (3–4)	*D* (4–5)	*E* (5–6)
Esotropia	2	8(89)*	6(67)*	12(52)*	13(54)*
Exotropia	–	1	–	2(9)*	2(8)*
No tropia	–	–	3(33*)	9(39)*	9(38)*

*In this Table the percentages are calculated for the total number of children with amblyopia in the same age group

Table III lists the prevalence of the different refractive errors associated with amblyopia in relation to the type of ocular deviation. There was a high incidence of hypermetropia,

Table III *Prevalence of different refractive errors in children with amblyopia in relation to type of ocular deviation (percentages in parentheses)*

		Refractive error					
		Hypermetropia		*Myopia*		*Astigmatism*	*Anisometropia*
Type of ocular deviation	*No. of cases*	*Less than 3D*	*3D and more*	*Less than 3D*	*3D and more*	*2 D and more*	*2 D and more*
Esotropia	41	11(27)	30(73)	–	–	6(14·6)	5(12)
Exotropia	5	–	1	2	2	3	2
No tropia	21	3(14)	12(57)	3(14)	3(14)	6(28·6)	13(62)

equal to, or more than 3 diopters, in cases of amblyopia without squint (57 per cent.) or associated with esotropia (73 per cent.). Astigmatism of 2 diopters or more was found in 14·6 per cent. of the children with esotropia and in 28·6 per cent. of those without strabismus. Anisometropia of 2 diopters or more was encountered more frequently in cases of amblyopia without ocular deviation (62 per cent.) than those with esotropia (12 per cent.). A group of five children showing amblyopia with exotropia was considered not to be of statistical significance and thus the prevalences of refractive errors in this group were not calculated.

Table IV shows the therapeutic results for the different age groups in terms of improved visual acuity. Since the number of very young children was small, the therapeutic results for Groups A and B were combined as one group treated before the age of 3 years. Only children with a follow-up period of at least 6 months after treatment were included in these results, and for this reason two children in age group E were excluded. A visual acuity of at least 6/12 or 3/9 was considered to be a good therapeutic result only if the difference in visual acuity between the normal and amblyopic eye was not more than one line. Good therapeutic results using the criteria described above, were obtained in 64 to 69 per cent. of the treated children in all age groups.

Table IV *Therapeutic results in terms of improved visual acuity, in each age group*

Age group (yrs)	*Number of cases*	*Good visual acuity obtained**	
		No.	*Per cent.*
A and B (1½–3) 472 + 1,438	11	7	64
C (3–4) 876	9	6	67
D (4–5) 1060	23	16	69
E (5–6) 1483	22**	15	68
Total	65	44	mean 67

*"Good visual acuity obtained" was defined as a visual acuity of at least 6/12 or 3/9, the difference in vision between the normal eye and the amblyopic eye being not more than one line.

**In this group two children were excluded because of a follow-up period of less than 6 months.

Of 46 children having amblyopia associated with squint, only twelve (26 per cent.) became alternators at the end of the treatment period.

Discussion

Opinion still differs regarding the prevalence of amblyopia in the general population; recorded incidences range from 1 to 5·3 per cent. (Downing, 1945; Cole, 1959; Helveston, 1965; Flom and Neumaier, 1966). These differences are based on the various methods and criteria employed. This is also evident when the findings of Gansner (1968) are studied. She examined 11,000 children between the ages of 4 and 8 years and found amblyopia in 2·2 per cent. However, when the diagnostic criteria for amblyopia were strict, *i.e.* visual acuity 6/18 or less, the incidence of amblyopia was found to be as low as 0·45 per cent.

Our findings indicate that, in pre-school children, there is a tendency for the prevalence of detected amblyopia to increase with age (Table. I) The hypothesis that the prevalence remains constant, can be rejected at the 1 per cent. significance level (according to the Mann-Whitney test with ties, Kendall, 1955), despite the fact that the differences between individual age groups are not significant. The low incidence of amblyopia in the younger children (1½ to 3 yrs) seems to be related mainly to the difficulty of diagnosing amblyopia at this age. Children less than 3 years old are not cooperative during the visual acuity tests and the acceptance of a difference in the child's behaviour when one eye is covered in comparison with the other as a diagnostic criterion also appears to be somewhat unreliable and inaccurate. Despite the fact that unilateral tropia may exist without amblyopia, the main diagnostic feature of amblyopia at this age is unilateral tropia, confirmed by the cover test; accordingly, cases of amblyopia without obvious tropia are often overlooked in small children. Table II shows that, after the age of 3 years, at least 33 per cent. of the cases of amblyopia do not squint, and all these cases were discovered by means of a visual acuity test. The increased prevalence of amblyopia without ocular deviation is due to the better cooperation of children at this age (Oliver and Nawratzki, 1971). As shown in Table III a high prevalence of anisometropia (62 per cent.) and/or astigmatism of 2 diopters or more was found in these cases.

A comparison of the therapeutic results shows that, until the age of 6 years, there are no great differences in the response of children of different age groups; in 67 per cent. of the children with amblyopia the visual acuity improved to at least 6/12. These findings are consistent with the therapeutic results reported by Scobee (1951), who studied 91 amblyopic children over 5 years of age, of whom 69 per cent. achieved a visual acuity of 6/12 (20/40) or more after therapy. Similar results were reported by Dowling (1942) and Kasser and Feldman (1953).

These findings suggest that up to the age of 6 years there is no critical period for the treatment of amblyopia as far as results are concerned. Therefore, it seems best to screen pre-school children at the age at which the greatest number of cases can be detected. Most children with amblyopia can be diagnosed at the age of 4 years and this is perhaps the best age for screening. There is little doubt, however, that early treatment of amblyopia has many advantages, including the prevention of the establishment of sensory anomalies. It is also a common experience that younger children accept amblyopic treatment more easily than older children and require a shorter period of treatment so that it is completed before they start school. Since it is doubtful whether screening at the age of 4 years can fulfil all these requirements, it seems advisable that the first screening should be performed at about the age of 3 years. At this age, all the cases of amblyopia associated with tropia will be diagnosed and possibly some of the non-squinting cases. The screening should be performed by orthoptists since professional skill and experience are required. Many amblyopic children without ocular deviation may be overlooked at the age of 3 years, and it is therefore advisable for an additional visual acuity test to be performed at kindergarten age (5 years), when children are generally cooperative and visual acuity tests can be performed with relative ease (Oliver and Nawratzki, 1971). Furthermore, screening at the kindergarten age, under standard conditions, can also be performed by relatively unskilled examiners, including kindergarten teachers and nurses who have not been specially trained for this purpose.

Summary

5,329 children aged 1½ to 6 years were screened for amblyopia and subsequently divided into five age groups. There was a significant increase in the prevalence of amblyopia with age, from 0·4 per cent. in the youngest to 1·6–2·1 per cent. in the oldest. Above the

age of 3 years, at least 33 per cent. of the patients with amblyopia did not squint and were diagnosed by means of visual acuity tests. They were probably not diagnosed earlier because of lack of cooperation.

Successful therapeutic results were obtained in about 67 per cent. of the cases and were similar in the various age groups. Until the age of 6 years, it appears that there is no critical age for the treatment of amblyopia, but a number of reasons appear to justify a screening test at the age of 3 years. Cases of amblyopia (mostly without squint) not diagnosed during this first screening period may be discovered later by a routine visual acuity test.

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Ocular side-effects of Ibuprofen

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Ibuprofen (2–4'-isobutylphenylpropionic acid) is an anti-inflammatory, analgesic, and antipyretic agent which is now frequently used in the treatment of rheumatoid and osteoarthritis. The drug is remarkably free of side-effects and no serious toxicity has been demonstrated in extensive clinical trials, apart from one case of gastrointestinal bleeding (Dick-Smith, 1969). Minor toxic effects which have been reported are listed in Table I (Boardman, Nuki, and Hart, 1967; Jasani, Downie, Samuels, and Buchanan, 1968; Thompson, Fox, and Newell, 1968; Chalmers, 1969; Dick-Smith, 1969).

Table I *Minor side-effects of Ibuprofen*

Gastrointestinal tract	Anorexia; nausea and vomiting; dyspepsia; upper abdominal pain; constipation
Skin	Irritation; rash
Central nervous system	Headache; giddiness; tinnitus; deafness
Miscellaneous	Tiredness; malaise; heavy perspiration; nocturnal frequency of micturition

No ocular side effects have been described in the literature. Recently two patients, whose case histories are reported below, presented at the Eye Clinic with visual disturbances related to Ibuprofen therapy, and as a result of this we examined a series of patients who were taking Ibuprofen, to assess the effects of the drug on ocular function. Our findings are reported.

Case reports

Case 1, a woman aged 71, was seen at the Eye Clinic in February, 1970, complaining of deteriorating vision, particularly in the right eye, over a period of 2 months. She had suffered from rheumatoid arthritis for 31 years and had been treated with an assortment of drugs including Plaquenil, which was stopped in November, 1968. When her vision started to deteriorate her treatment was prednisolone 5 mg. daily, a dose which had remained unaltered for 9 months, and Ibuprofen 0·4 g. daily, which she had been taking for 8 months. She had received a total of 90 g. Ibuprofen at the time of presentation.

Examination

The corrected visual acuity of the right eye was 6/18 and of the left 6/9. The media were clear and the fundi normal. A visual field examination, performed on the Goldmann perimeter, revealed a centrocaecal scotoma in the right eye (Fig. 1) and an enlargement of the blind spot in the left (Fig. 2).

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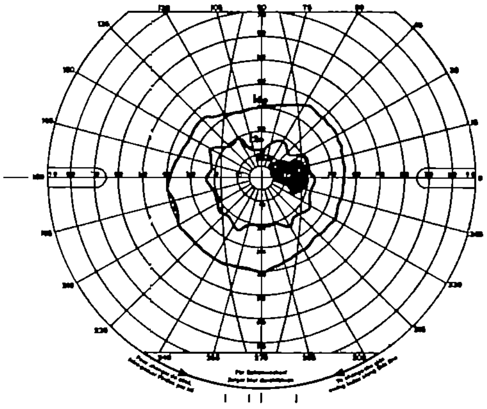

FIG. 1 *Visual field of right eye in Case* 1

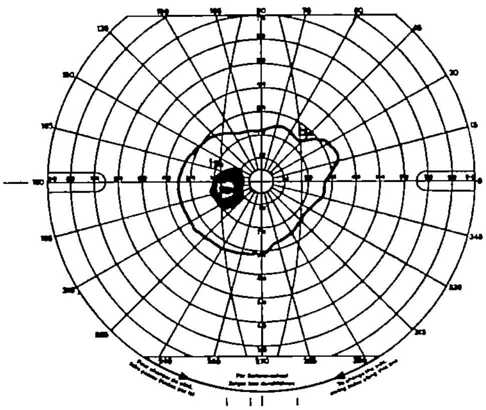

FIG. 2 *Visual field of left eye in Case* 1

Treatment

Ibuprofen was thought to be the cause of the reduced visual acuity and visual field defects, and was therefore withdrawn. The patient reported an immediate improvement in her vision and one month, later although she still complained of some residual dimness of vision, the visual acuity had improved to 6/9 in the right eye and 6/6 in the left.

Result

This improvement was maintained, and when the visual fields were examined in August, 1970, the defects had disappeared and the fields were full. The vision then was 6/6 in both eyes unaided.

Case 2, a 67-year-old woman, was seen at the Eye Clinic in June, 1970, because of the sudden appearance of "a moving mosaic of coloured lights in front of both eyes". Her medication at that time was digoxin 0·25 mg. twice daily, Lasix 80 mg. three times a day, Etophylate 500 mg. three times a day, Aldactone A 25 mg. daily, Tofranil 25 mg. three times a day, and Eltroxin 0·1 mg. three times a day. None of these drugs had been increased in dosage or added to her treatment within the previous 3½ weeks, but 7 days before her visit to the Eye Clinic she had started on Ibuprofen 200 mg. three times a day for arthritis of the sacroiliac joints and within 2 days the coloured mosaic appeared and gradually increased in intensity.

Ocular examination

No abnormality was found and, as it was thought that the symptoms could be due to Ibuprofen, this drug was withdrawn. There was an immediate decrease in the intensity of the symptoms and the vision had returned to normal in 11 days.

Investigation of patients on Ibuprofen

38 patients receiving Ibuprofen were examined. The visual acuity, fundus, and visual fields, including macular sensitivity, were assessed. The findings are summarized in Table II (overleaf).

Discussion

The first patient, who was on treatment with Ibuprofen, presented with reduced visual acuity in both eyes, an early centrocaecal field defect on the right side and an enlarged blind spot on the left. On withdrawal of the drug the visual acuity returned to normal and the visual field defects disappeared. This is the typical presentation of a toxic amblyopia. Harrington (1964) has listed a number of agents which can cause a central

Table II *Summary of investigations of* 38 *patients on Ibuprofen*

Case no.	*Diagnosis*	*Duration of Treatment (mths)*	*Sex*	*Age (yrs)*	*Dose (g./day)*		*Other drugs*
					Current	*Total*	
3	RA	3	F	46	0·6	50G	Indocid; predisone
4	RA	12	F	54	1·2	353	Tofranil; Mandrax
5	RA	1	F	74	Nil	13	Distalgesic
6	RA	18	F	62	0·6	303	Plaquenil; Indocid
7	RA	12	F	43	0·8	202	Nil
8	RA	12	M	61	0·6	202	Gold; disprin
9	RA	6	F	48	0·8	168	Plaquenil
10	RA	20	F	49	0·6	360	Predisolone; Indocid; Lasi
11	RA	18	M	49	0·6	324	Plaquenil
12	RA	7	F	58	Nil	118	Nil
13	RA	24	F	57	0·8	470	Nil
14	RA	2	F	65	1·2	67	Digoxin; predisolone
15	RA	5	F	64	0·6	83	Gold
16	RA	3	F	63	1·2	101	Predisone; gold; aspirin
17	RA	1 wk	M	68	0·6	3	Predisolone
18	RA	6	M	43	1·0	146	Mandrax
19	RA	5	F	60	0·8	157	Aspirin
20	RA	16	F	72	Nil	358	Nil
21	RA	4	M	65	0·6	67	Digoxin; Aldactone; Lasix
22	RA	9	M	61	1·0	237	Valium; Avomine
23	RA	6	F	40	1·2	202	Plaquenil
24	RA	6	M	64	0·6	101	Plaquenil
25	RA	4	F	48	1·2	136	Plaquenil; gold
26	RA	4	F	58	1·2	135	Aspirin; Betamethasone
27	RA	4	F	42	1·2	125	Plaquenil; Phenylbutazone
28	RA	12	F	49	0·6	230	Aspirin; Nucil
29	RA	2	M	58	0·8	45	Nil
30	RA	7½	F	13	0·4	84	Nil
31	RA	9	F	16	0·2	22	Plaquenil
32	RA	4	F	58	0·8	111	Nil
33	RA	6	M	59	0·4	67	Nil
34	RA	1	F	59	0·6	17	Nil
35	RA	5	F	38	0·8	111	Decadron
36	RA	10 days	F	73	0·6	6	Nil
37	OA	21	F	69	0 6	353	Plaquenil
38	PA	6	M	21	0·6	110	Librium
39	PA	8	F	35	1·2	184	Indocid; aspirin
40	SC	6	M	60	0·6	83	Nil

RA : Rheumatoid arthritis OA : Osteoarthritis PA : Psoriatic arthropathy SC : Supraspinalis condylitis

istory of visual disturbance	*Corrected visual acuity*		*Fundi*	*Visual fields*	*Remarks*
	Left	*Right*			
-	6/4	6/4	N	N	
-	6/4	6/6	N	N	
all in left visual acuity ter 3 wks Ibuprofen	6/18	6/60	Bilateral circinate retinopathy R > L	Right normal Left central scotoma	See Discussion
-	6/6	6/6	N	N	
-	6/6	6/6	N	N	
-	6/6	6/5	Peripheral retinal degeneration	N	
-	6/5	6/6	N	N	
	6/6	6/5	N	N	
-	6/4	6/4	N	Reduced central retinal sensitivity	
-	6/6	6/6	N	N	
-	6/6	6/6	N	N	
ilateral fall in vision after wks Ibuprofen	6/18	6/18	Bilateral macular pigment changes	Bilateral centrocaecal scotoma	See Discussion
-	6/9	6/6	N	N	
-	6/9	6/5	N	N	
-	6/6	6/4	N	N	
-	6/6	6/6	N	N	
-	6/9	6/9	N	N	
-	6/18	6/6	N	Reduced sensitivity	Bilateral lens opacities
-	6/4	6/6	N	N	
-	6/5	6/5	N	N	
-	6/6	6/6	N	N	
-	6/6	6/4	N	N	
-	6/5	6/4	N	N	
-	6/6	6/6	N	N	
-	6/4	6/4	N	N	
-	6/5	6/5	N	N	
	6/5	6/5	N	N	
-	6/4	6/4	N	N	
-	6/4	6/4	N	N	
-	6/5	6/12	N	N	Old left iritis
-	6/4	6/9	N	N	
-	6/5	6/6	N	N	
-	6/4	6/4	N	N	
lurred vision after 5 days ouprofen	6/6	6/6	N	N	See Discussion
-	6/6	6/6	N	N	
-	6/4	6/4	N	N	
-	6/4	6/4	N	N	
	6/9	/69	N	N	

or centrocaecal scotoma, including tobacco, ethyl alcohol, methyl alcohol, lead, carbon disulphide, iodoform, thallium, digitalis, chloramphenicol, plasmocid, streptomycin, sulphonamides, and isoniazid. The exact site of the toxic action is unknown in most cases and may be situated in the retina, the optic nerve, or even further back in the post-chiasmal section of the visual pathway. Usually the amblyopia induced by the agent is reversible on withdrawal of the drug but permanent visual loss may occasionally result.

The second patient, who was seeing a mosaic of lights, was receiving a variety of drugs at the time of onset of her symptoms, including digoxin, which can cause visual hallucinations, scintillations, and xanthopsia. The onset and regression of symptoms, however, were so closely related to the commencement and withdrawal of Ibuprofen that we have little doubt that this drug was responsible. This type of visual disturbance is almost certainly cortical in origin and is unrelated to the toxic amblyopias.

Three patients of the 38 examined in the survey had visual disturbances which they related to Ibuprofen. In Case 5 bilateral circinate retinopathy explained the reduced visual acuity and, although she had a reduction in vision within 3 weeks of starting Ibuprofen, we do not think that it is justified in this case to relate the drug to the visual disturbance. In Case 14 there were also macular changes but these were of the senile type, and were first recorded in 1964, at which time the visual acuity had been normal. When she presented with her recent visual failure, after being on Ibuprofen for 2 months, the visual acuity was 6/18 in both eyes and visual field examination on the Goldmann perimeter showed bilateral centrocaecal defects. When the drug was withdrawn there was an immediate subjective improvement in her vision and this was confirmed not only by an improvement in the visual acuity to 6/9 in each eye but also by the disappearance of the centrocaecal field defects. A minute paracentral scotoma persisted in each field, however, and this was consistent with her preexisting maculopathy. There seems little doubt that this patient's visual deterioration was related to Ibuprofen therapy, although the clinical picture was complicated by the maculopathy.

In Case 36 blurring of vision developed a few days after starting treatment with Ibuprofen for a rheumatoid synovitis of the left wrist. After 10 days of treatment her ocular symptoms had not improved and she stopped taking the drug. She did not consult her doctor and her vision returned to normal within the next few days. She was not referred to the Eye Clinic until 7 weeks later at which time the ocular examination showed normal results. This patient may have had a toxic reaction to Ibuprofen though this supposition is based entirely on her subjective history.

In summary, therefore, Patients 1 and 14 developed centrocaecal field defects and reduced visual acuity while on Ibuprofen therapy, and in both there was a marked improvement when the drug was withdrawn. Although in Case 14 there was a pre-existing maculopathy, we believe that both patients had a toxic amblyopia due to Ibuprofen. In Cases 5 and 36, a toxic reaction may have taken place, but the evidence is not conclusive. The symptoms exhibited by Patient 2 are unrelated to those of the previous four cases, and are probably cortical in origin.

Summary

Two patients with ocular symptoms related to Ibuprofen therapy are reported and the findings in a survey of 38 patients taking this drug are discussed.

Our thanks are due to Mr. M. V. Graham, Mr. P. A. Graham and Dr. K. Lloyd for allowing us to study their patients.

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Subconjunctival gentamicin

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Gentamicin sulphate is a new broad spectrum antibiotic produced by *Micromonospora purpurea*, and is active against both Gram-positive and Gram-negative bacteria.

The antibiotics which have hitherto been used subconjunctivally all have some disadvantages. Penicillin, which is only mildly irritant, has a range of activity which does not cover the Gram-negative bacilli, *Pseudomonas*, *Proteus*, or *E. coli*. In addition, most strains of staphylococci may become resistant. Streptomycin is useful but resistant strains develop quickly. Polymyxin and Neomycin are rarely used because the injections are painful and irritant to the tissues.

Soframycin is a useful antibiotic, being active against both Gram-positive cocci and Gram-negative bacilli, but repeated injections are slightly irritant to the tissues and systemic absorption may have nephrotoxic and ototoxic effects.

ADMINISTRATION

The use of gentamicin in the form of local ocular drops is now established. It has also been given intrathecally, and to rabbits subconjunctivally (Furgiuele, Kiesel, and Martyn, 1965). We have now administered this antibiotic subconjunctivally in man to assess its usefulness in ophthalmology.

Gentamicin sulphate is highly stable and water soluble, and when given in a dilution of 20 mg./ml. subconjunctivally, it produces an osmotic pressure in solution which is less than that of the other antibiotics; better diffusion and local tolerance can therefore be anticipated.

The osmolarities of different antibiotics are tabulated below according to a theoretical assumption based on molecular weight and drug concentration.

Antibiotic	*Concentration*	*Percentage ionic tonicity (g./ml.)*
Gentamicin	20 mg./ml.	50
Penicillin	0·5 mega units/ml.	55
Streptomycin	0·25 g./ml.	180
Soframycin	250 mg./ml.	300
Neomycin	500 mg./ml.	600

The activity of gentamicin sulphate is enhanced when it is used synergistically with ampicillin, chloramphenicol, colistin and tetracycline.

ASSESSMENT

The trial was conducted in three parts:

(1) *Tolerance*

To determine the response to a single subconjunctival injection of 20 mg. gentamicin (1 ml.) as regards local reaction and pain, ten patients received a subconjunctival injection of gentamicin

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*Present address. Royal Hospital, Sheffield sulphate infero-temporally at the conclusion of a routine cataract extraction. After 3 hours the patients were asked whether they had any pain in the area of the injection. At the first dressing (24 hrs after the injection) the area was examined for any reaction.

One patient complained of pain, localized to the area of the injection, and six showed minimal conjunctival injection and chemosis which disappeared after a further 24 hrs.

(2) *Prevention of infection*

Five patients were given subconjunctival injections of 20 mg. gentamicin sulphate at the conclusion of an operation for a perforating injury; there was no case of postoperative infection.

(3) *Treatment of established infection*

In eight patients the conjunctival sac was anaesthetized with 4 per cent. cocaine drops locally, and gentamicin was injected subconjunctivally as shown in the Table.

Table *Results of subconjunctival injection of gentamicin in eight cases of ocular infection*

Case no.	*Diagnosis*	*Bacteriology*	*Subconjunctival gentamicin*	*Result*
1	Stitch abscess in aphakic subject with 2 mm. hypopyon and early vitreous abscess	No growth	20 mg. + mydricaine 2 gutt. gentamicin four times daily Repeat 20 mg. after 24 hrs + systemic chloramphenicol	Hypopyon cleared in 6 hrs Healed in 9 days
2	Corneal ulcer (spontaneous) with 3 mm. hypopyon	No growth	20 mg. + mydricaine 2 + systemic ampicillin Gentamicin repeated twice	Hypopyon cleared in 3 days Healed in 5 days
3	Corneal ulcer with 3 mm. hypopyon in aphakic Had been treated with local steroids for 1 week before admission	*Strept. viridans*	20 mg. gutt. gentamicin 1 per cent. 1-hrly + systemic chloramphenicol	Hypopyon cleared in 36 hrs Healed in 10 days
4	Corneal abscess (traumatic) 2 mm. diameter	No growth	20 mg. repeated in 3 days gutt. gentamicin 1 per cent. 1-hrly + systemic ampicillin 6-hrly	Healed in 6 days
5	Infected corneal wound after cataract extraction	No growth	20 mg. repeated in 2 days gutt. gentamicin 1 per cent. 1-hrly	Exudate on anterior vitreous face cleared in 48 hrs Healed in 4 days
6	Corneal ulcer (spontaneous) with 3 mm. hypopyon	No growth	20 mg. gutt. gentamicin 1 per cent. 1-hrly	Healed in 3 days
7	Infected wound after cataract extraction	No growth	20 mg. gutt. gentamicin 1 per cent. 1-hrly	Healed in 24 hrs.
8	Corneal abscess (post-dendritic) with 2 mm. hypopyon	No growth	20 mg. gutt. gentamicin 1 per cent. 1-hrly + systemic ampicillin	Healed in 4 days

Results

Subconjunctival gentamicin was found to be well tolerated locally. There were no cases of postoperative infection when the gentamicin was used prophylactically in five cases of perforating injury, and eight cases of corneal infection treated with subconjunctival gentamicin all responded satisfactorily.

Mydricaine 2 (6 mg. procaine hydrochloride, 1 mg. atropine sulphate, 5 mg. acid boric, 0·12 ml. solution of adrenaline 1/1000) was added to the gentamicin with no adverse effect. Incubation of gentamicin with Mydricaine 2 at 37°C. for 48 hrs showed that the solution was stable and there was no reduction of the adrenaline.

Discussion

Subconjunctival gentamicin is well tolerated locally and produces very little chemosis. This lack of irritation to the conjunctiva is important in assessing the degree of inflammation of the eye.

The value of subconjunctival gentamicin as a prophylactic measure for perforating injuries is doubtful, since induced allergic reactions and acquired bacterial resistance may become significant problems (Gordon, 1970), but if wounds are contaminated with *Pseudomonas* or other pyogenic organisms, subconjunctival gentamicin is useful.

Summary

The purpose of this communication is to establish that treatment with gentamicin may be effective in infective conditions, and the rapidity of the response leads us to believe that it is more effective than the antibiotics in use at present. A double-blind trial would be necessary to confirm this.

We should like to thank the consultants of the Bristol Eye Hospital for kindly allowing us to treat their patients, Prof. D. A. Norton for compounding the subconjunctival solutions and supplying the data on osmotic pressures, and Dr. I. W. Jamieson of Aspro-Nicholas Laboratories for providing the gentamicin.

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Experimental marginal corneal infiltrates

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Marginal infiltrates arise from a wide variety of causes and according to the recent literature occur most commonly in association with chronic staphylococcal blepharitis. Marginal infiltrates often have a crescent form or coalesce to form a complete ring concentric to the limbus. On the other hand, the well-formed manifestation of an immunological process in the cornea, the so-called immunological corneal ring, often strikingly resembles marginal infiltration in man (Germuth 1959). This has given rise to the presumption that marginal infiltrate, when associated with staphylococcal lid inflammation, is a result of hypersensitivity reaction in which staphlyo-antigen plays an important role (Thygeson, 1969).

Hogan, Diaz-Bonnet, Okumoto, and Kimara (1962) tested this hypothesis experimentally. Their animals were immunized with subcutaneous staphylococcal antigen with the addition of Freund's adjuvant. Immunological rings developed clinically with marked uveitis. Microscopical examination showed these infiltrates to be composed of neutrophils. The results of these experiments are very important in the studies of staphylococcal corneal disease, but the clinical appearance differs from that of a marginal infiltrate in man, because in human disease the antigen enters the organism not subcutaneously but through the cornea and/or conjunctiva, so that there is no marked uveal reaction. Also Freund's adjuvant affects the potency of the staphylococcal antigen.

The experiment presented in this paper was undertaken in an effort to produce an immunological ring using staphylo-antigen without the help of Freund's adjuvant and introducing it directly into the cornea.

Material and methods

EXPERIMENTAL ANIMALS

Fifteen chinchilla rabbits weighing from 2 to 2·5 kg. were divided into three groups of five animals. The eyes of all the animals were examined for anterior lesions before the experiment was begun.

ANTIGEN

Staphylococcal antigen was prepared from a strain of coagulase-positive *Staphylococcus aureus* isolated from the lid margin of a patient with staphylococcal blepharitis associated with marginal infiltrate. 1 g washed bacteria was suspended in 10 ml. 0·9 per cent. NaCl solution to which an equal volume of 0·15 M phosphate buffer pH 7·7 was then added. The mixture was boiled under reflux for 3 hrs and allowed to stand at 37°C. overnight. The bacterial cells were deposited by centrifugation and discarded and 2 volumes of cold ethanol were then added to the supernatant. The resulting precipitate was then redissolved in 10 ml. 0·9 NaCl solution (Hall, Smith, Edwards, and Shooter, 1969).

IMMUNIZATION

(1) Five animals were immunized by subcutaneous administration of antigen together with Freund's adjuvant for 24 days. At 3-day intervals the animals were given increasing doses of

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antigen and adjuvant (beginning with 0·2 and going up to 2 ml.); 30 days after the beginning of immunization antibodies were searched for.

(**2**) Five animals were immunized by intraperitoneal injections. The doses of antigen and time intervals were the same as in the first group with the following differences: Freund's adjuvant was not used and booster injections were given 40, 50, and 60 days after the beginning of immunization.

(**3**) Five animals received intralamellar injections of 0·5 ml. antigen into the centre of the cornea.

The animals of the first and the second group were challenged by intralamellar injection of antigen after 30 and 60 days respectively. Those in the third group were not challenged.

The presence of antibodies was demonstrated by agar diffusion and precipitation technique.

Results

SUBCUTANEOUS IMMUNIZATION WITH FREUND'S ADJUVANT

After they were challenged all the animals in this group developed a more or less marked uveal reaction with fibrin deposits and cells in the anterior chamber. In two animals a semilunar infiltrate was seen separated from the limbus by a clear zone.

PROLONGED INTRAPERITONEAL IMMUNIZATION WITHOUT FREUND'S ADJUVANT

More or less severe uveitis was seen in all animals after they were challenged, but in all of them a dense, diffuse corneal infiltrate appeared at the site of injection. Three developed a ring-like marginal infiltrate after 24 hours.

CORNEAL IMMUNIZATION

All the eyes in this group were quiet until the 14th day when in two animals ring-like marginal infiltrates appeared accompanied by a few cells in the anterior chamber. The pupil was somewhat dilated and its reaction was sluggish (Fig. 1).

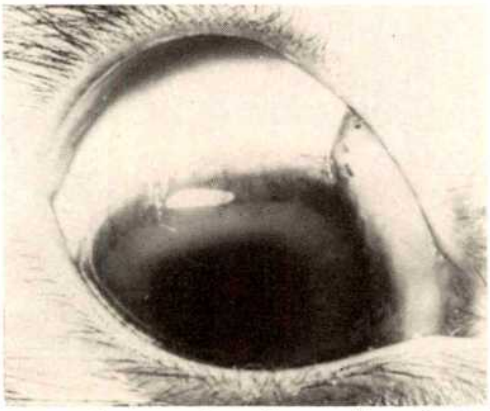

FIG. 1 *Appearance of eye after corneal immunization*

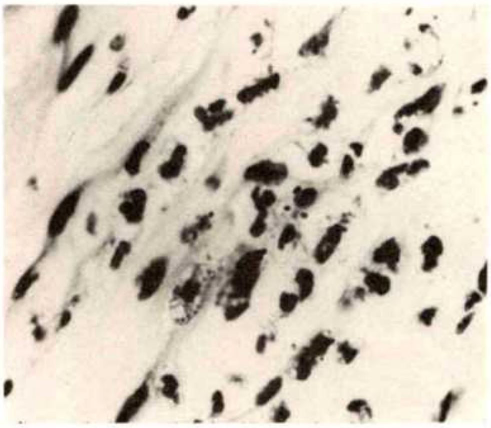

FIG. 2 *Plasma cells and plasmocytoid cells.* ×360

The eyes were enucleated and subjected to microscopical examination. The material was stained with haematoxylin and eosin and plasma cells differentiated by the methyl-green-pyronin technique. The limbal zone of the cornea showed a heavy plasma cell infiltration. There were also many plasmocytoids in the corneal infiltrate. These cells were packed with coarse eosinophilic granules and had pyknotic nuclei (Fig. 2). The corneal infiltrate was well demarcated at the centre of the cornea and disappeared gradually towards the limbus; there was no necrosis.

Discussion

It is apparent that the intensity and the form of immunopathological reaction in the eyes of the animals in this experiment were directly dependent on the route of antigen administration and the duration of the immunization. Marginal infiltrates appeared in those immunized with and without adjuvant, but after a much longer time in the second group. *Staphylococcus aureus* has relatively weak antigenic properties, so that either the addition of adjuvant or prolonged immunization is needed. In the human staphylococcal infection, marginal infiltrates appear after the disease had been present in the eyelid for several years.

The reactions in the systematically immunized animals differ from those in intracorneally immunized animals. The route of administration is important in determining the form and intensity of the hypersensitivity reactions. Klinge and Vaubel (1931) discovered that the tissues which first come into contact with the antigen are first sensitized. Immunization *via* the cornea is what happens in patients with staphylococcal blepharitis whose corneae are constantly exposed to the *Staphylococcus* and its antigens. In these experiments we were also able to elicit clear-cut corneal reactions with minimal uveal irritation and this is also a feature of marginal infiltrates in man If the antigen enters the organism through the cornea, only marginal infiltrates appear, but if the immunization is parenteral, diffuse uveal and corneal reactions are seen.

Therefore, it may be postulated that under natural conditions, in the eye suffering for a long time from staphylococcal blepharoconjunctivitis, small quantities of staphylococcic antigen constantly enter the circulation through the cornea and conjunctiva and lead to the formation of antibodies. When these antibodies reach the cornea an immunological reaction takes place and is seen as a marginal infiltrate in the otherwise transparent cornea. The presumption that corneo-conjunctival application of an antigen can lead to the state of local hypersensitivity was proved by both Chait (1950) and Aronson, Goodner, Yamamoto, and Foreman (1965).

Summary

An attempt has been made to investigate the hypothesis that marginal infiltrates may result from corneal hypersensitivity to staphylococcal antigen. It was possible to produce marginal infiltrates in experimental animals by using staphylococcal antigen. It was also possible to elicit a corneal reaction resembling that seen in man, but only if the immunization was obtained *via* the cornea; in systemically immunized animals marked uveal and diffuse corneal reactions occurred as well as marginal infiltrates.

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Impacted microfilaria in the lens capsule

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Filariae are threadworms belonging to the class Nematodes. Their immediate hosts are certain species of mosquitoes and flies, which are found mainly in Asia, Africa, and Central America. When transferred to man the parasites settle in one particular organ of the body, which varies according to the variety of filaria. There they produce larvae known as microfilaria which, in certain species, pass into the blood and may be readily detected in thick-drop preparations (Sandoz, 1952).

In equatorial Africa, it has been reported that there are half a million filarial patients who are blind (Choyce, 1964). With the exception of trachoma, filariasis is responsible for more loss of sight than any other infection (Ridley, 1963).

Living adult worms of *Wuchereria bancrofti* (*F. bancrofti*), which may be as much as one inch long, have been observed in the vitreous (Nayar and Pillai, 1932) and in the anterior chamber of the eye (Nayar and Pillai, 1932; Wright, 1934; Fernando, 1935; Tawara, 1936). In most cases there was associated iridocyclitis. In addition, *Microfilaria bancrofti*, which are only about 280 μ long, have been seen actively moving in the anterior chamber (Sun, 1958; Desprez, 1959; Subramanian and Ram Mohan, 1966). According to Choyce (1964), *Microfilaria volvulus* has been reported attached to the lens capsule by only two writers (Torroella, 1962; Gunders and Neumann, 1963). The last-named authors claimed that they detected living embryos within the lens capsule.

Case report

A male Indian doctor aged 39, attended the eye department as out-patient on May 27, 1969. His main complaints were blurred vision together with redness of the left eye of 3 day's duration.

He gave a history of two episodes of acute iritis in the left eye, the first in 1964 in India; the second in 1968 in the United Kingdom. The latter episode was complicated by raised intraocular tension, which was controlled with Diamox tablets, and topical Atropine and Betnesol.

He had enjoyed reasonably good health until the beginning of 1968, when he began to experience increasing lassitude and lethargy.

Physical examination

The patient was healthy looking, well nourished, but slightly obese. Lymph nodes were not palpable. The liver was palpable two fingers' breadth below the right costal margin. There was no subcutaneous nodule and no evidence of elephantiasis of the lower limbs or scrota. Radiology of the chest showed no abnormality. Urine and stool examinations were negative. Tests for liver function were within normal limits.

Total serum protein 7·9 g./100 ml.; serum albumin 4·7 g/.100 ml.; serum globulin 3·2 g./100 ml.; serum bilirubin 1·0 mg./100 ml.; alkaline phosphatase 6·5 K.A. units; zinc sulphate turbidity 10·4 units; SGOT 30 units.

Ocular examination

The visual acuity was 6/6 and N·5 unaided in the right eye, and 6/6 partly and N·5 unaided in the left. The left eye showed slight circumcorneal ciliary injection. The pupil was transversely oval in shape. Slit-lamp microscopy revealed a slight aqueous flare in the anterior chamber. No cells

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or keratic precipitates could be detected. There were a few patches of iridic pigment on the anterior lens capsule. Situated above one of the patches in the 7 o'clock position was a minute, whitish, thread-like organism with one end adherent to the anterior lens capsule and the free end showing active continuous, wriggling movements in the anterior chamber (Figs 1 and 2). Ophthalmoscopic examination revealed no abnormality. The ocular tension was normal.

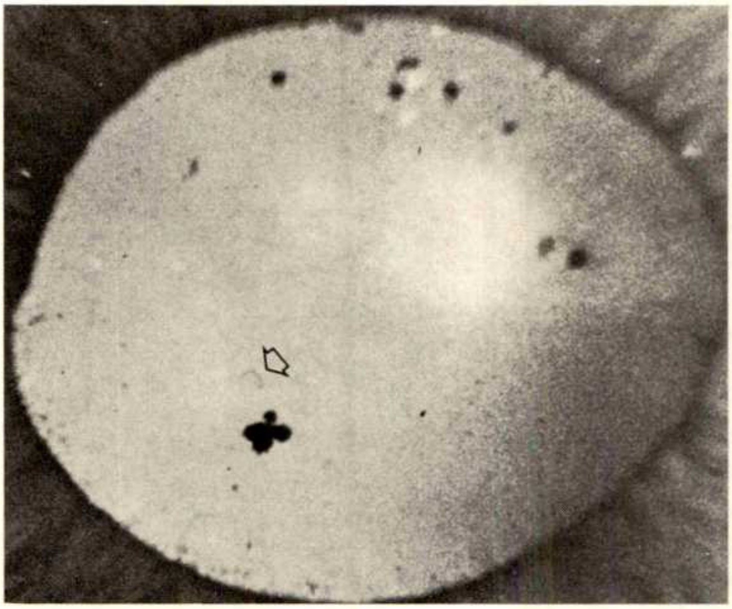

FIG. 1 *Microfilaria on anterior lens capsule (arrow)* ×20

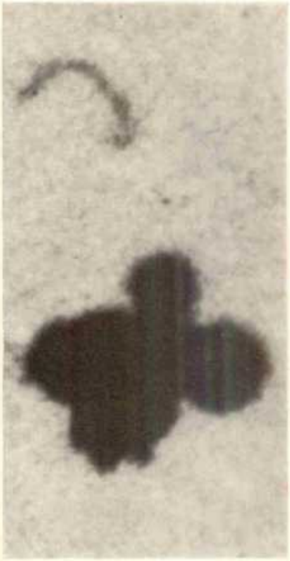

FIG. 2 *Higher-power view of same.* ×85

Laboratory investigations

The report of the full blood investigation was a follows:

Haemoglobin 17 g per cent.

White cells 6,100/c.mm; differential: neutrophils 3,360/c. mm (55 per cent.), lymphocytes 2,074/c.mm (34 per cent.), eosinophils 310/c.mm (5 per cent.), monocytes 366/c.mm (6 per cent.), basophils nil.

Red cells normochromic and normocytic. Platelets adequate. No evidence of eosinophilia.

Examination of the midnight sample of peripheral blood revealed *Microfilariae bancrofti* in small numbers in the ordinary specimen of peripheral blood, and numerous in the formalized concentrated peripheral blood specimen (Fig. 3).

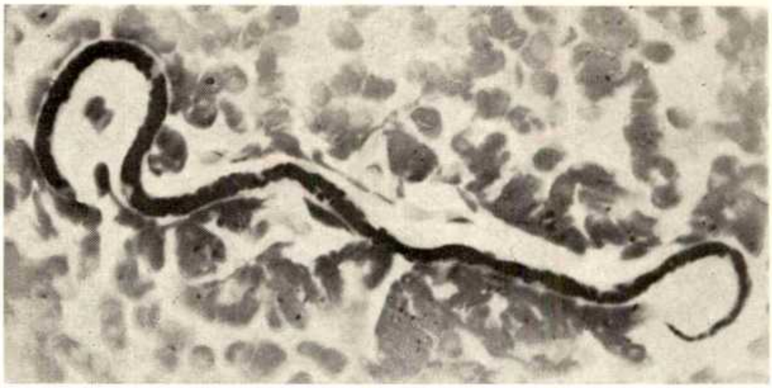

FIG. 3 *Microfilaria in peripheral blood.* ×580

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Treatment

A 3 week-course of diethylcarbamazine (Banocide) tablets 2 mg./kg. body weight three times a day was given, after which the midnight peripheral blood examination was repeated, and some microfilariae were still present. Slit-lamp examination of the left eye showed that the microfilaria was still actively motile on the anterior lens capsule.

According to Duke-Elder and Perkins (1966), atropine may restrict the movements and kill the worm (López, 1891; Schnaudigel, 1922), but pilocarpine apparently irritates it and makes it burrow deeper into the tissues (Gabriélidès, 1938). On June 22, 1969, Atropine 1 per cent. eyedrops were instilled into the left eye, and on the following day the microfilaria was found to be lifeless and immobile. As a prophylactic measure Betnesol eyedrops were instilled four times a day, and after one week, no trace of the organism could be seen, and the eye remained quiet.

Follow-up

Another two courses of Banocide tablets were subsequently given, and when the patient was last examined (in May, 1970) there was no inflammation in the eye, but the peripheral blood still showed a small number of microfilariae in the concentrated specimen.

Discussion

Gunders and Neumann (1963) appear to be the only authorities to have observed motile microfilaria within the lens capsule. We present photographic evidence of a similar case showing the microfilaria of *W. bancrofti* adherent to the lens of a 39-year-old man. The lens capsule seems to be an impassable barrier to the microfilaria in most instances (Choyce, 1964), but partial penetration had occurred in this case. The lethal effect of atropine on the microfilaria was confirmed.

Summary

A 39-year-old man presented with a microfilaria attached to the anterior lens capsule of the left eye. The management of the case is described.

We wish to thank Dr. J. W. Whitelaw, consultant haematologist to the Southern General Hospital, Glasgow, for examining the blood specimens, and for permission to publish Fig. 3., and Dr. J. Williamson, consultant ophthalmologist to the Southern General Hospital, Glasgow for his helpful criticism in the preparation of this paper.

We are also grateful to Mr. J. Ibbott, senior optician, and Mr. A. Blacklock of the Department of Medical Photography and Illustration, Southern General Hospital, Glasgow, for taking the photographs.

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Bleeding from the conjunctiva

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The discovery of frank bleeding from the conjunctiva, apart from injury, is a relatively rare condition, but it is not infrequent to find a sanguinous discharge in cases of severe inflammation of the conjunctiva.

The various causes of bleeding from the conjunctiva are vicarious menstruation, haemophilia, anaemia, jaundice, vascular tumours, bleeding from the lacrimal gland, regurgitation of blood from the nose through the lacrimal passages, and hysteria.

Spontaneous bleeding from the conjunctiva occurs in cases of vicarious menstruation, the weeping of "bloody tears" (lacrimae cruentae, dacryohaemuhysis: Duke-Elder, 1965); this is mainly of historical interest, extragenital haemorrhages taking place at periodic intervals corresponding to the menstrual cycle (Novak and Jones, 1961).

Vicarious menstruation from the eyes was recorded very early by Dodonaeus (1581) and Kersten (1841). Cases in which recurrent ocular haemorrhages can be correlated with menstrual somatic readjustment have been reported by Jüngken (1842), Mackenzie (1854), Pascal (1888), Greig and Kynoch (1912), Gabriélidès (1923), Greig (1932), Poos (1933), François (1934), Dejean (1934), Tóth (1944), and Polychronakos and Leanis (1956).

Haemophilia has been described by various authors, where bleeding from the eyes was initiated by a slight trauma, and was even fatal (Schmidt-Rimpler, 1887). Death from haemorrhage also followed the application of silver nitrate to the conjunctiva in the newborn (Müller, 1893; Abbe, 1899; Hansell, 1900; Wiener, 1903; Heal, 1928).

Other cases of alarming conjunctival bleeding were recorded in anaemic patients by Fischer (1832) and Cross (1891) and in a jaundiced patient by Havers (1964).

The presence of vascular tumours in the conjunctiva has been found to be a cause of conjunctival haemorrhage. Jessop (1895) recorded a patient in a state of collapse due to haemorrhage from an ulcerated angioma in the upper lid. Other cases have been reported by Mathieu (1894), de Micas (1908), Wallis (1916), James and Trevor (1918), Maxted (1919), White (1945), Bakker (1948), Ash (1950), and Nirankari and Singh (1961).

Conjunctival haemorrhage may arise in certain cases from the lacrimal gland (Lindemann, 1920), and from regurgitation of blood from the nose, through the lacrimal passages, issuing usually through the inferior punctum (Duke-Elder, 1965). It has been noted in epistaxis, either spontaneously (Jongkees, 1941), after nasal tamponage (Konikow, 1916; Messner, 1947), or after a nasal fracture (Valière-Valeix, 1939; Urbantschitsch, 1946).

The condition has also been seen in cases of hysteria (Huss, 1857; Damalix, 1882; Hynek, 1932,) and after gross disturbances of the autonomic nervous system (Bolotte and Fribourg-Blanc, 1931).

Conjunctival haemorrhage may also occur in healthy persons, with little or no cause apart from stooping (Perlia, 1888; Cross, 1891) or muscular effort (Denti, 1883); Minchin (1935) reported it in a child after copious weeping.

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Case report

A girl aged 17 years came to the out-patients clinic of the Ophthalmic Hospital at Tanta, complaining of recurrent bleeding from the eyes. This had started 8 months previously, when blood had suddenly appeared in the eyes, in conjunction with the menstrual cycle. The conjunctival bleeding was at times so severe as to spill over from the lower lids and cover the cheeks, but usually the blood only streaked from the medial angles. Besides this cyclic conjunctival bleeding, the patient had also noticed 2 months ago, that sudden bleeding occurred when she was nervous or angry. The intercyclic bleeding was not severe, amounting to only a few drops which at times occurred two or three times in a day. Epistaxis occasionally accompanied the conjunctival bleeding. The patient's normal tears were not tinged with blood. She had menstruated regularly since the age of 12.

There was a history of jaundice 1 year before, and of four epileptic fits in the previous 12 months. An appendicectomy had been done 2 months before she came to the clinic.

EXAMINATION

The patient presented with a streak of blood flowing down from the medial canthus, along the nasojugal furrow (Figure). The eyes were examined for a source of the bleeding. The conjunctiva appeared strikingly "white", with no evidence of congested vessels in the bulbar or palpebral conjunctiva. She was admitted to hospital, and the eyes were examined each time the bleeding occurred.

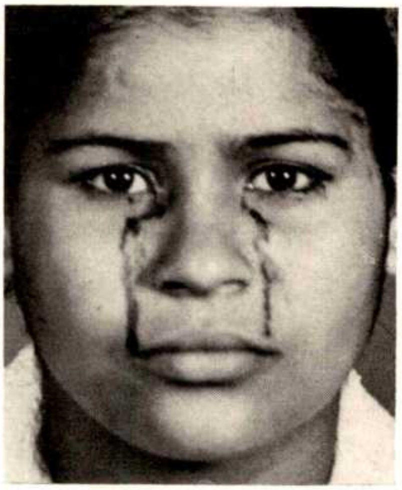

FIGURE *Vicarious menstruation from the conjunctiva*

The whole conjunctival sac was seen to be oozing blood, which streaked down the cheeks, leaving the eye white as before. Slit-lamp examination revealed no pathological lesion. Fundus examination was normal, and the ocular tension and visual fields were within normal limits.

The visual acuity was 6/18 in both eyes without glasses, and 6/6 with correction, right eye −0·25 D sph., −0·5 D cyl., axis 180°; left eye −0·5 D sph., −0·5 D cyl., axis 180°. Colour vision was normal. The lacrimal gland and passages were normal and patent on syringing.

Thorough medical, gynaecological, and ear, nose and throat examinations were performed, but no cause for the bleeding could be found. The patient was unstable, nervous, and easily agitated.

INVESTIGATIONS

A complete blood examination gave the following results:

Red blood cells 3,120,000/c.mm.

Haemoglobin 60 per cent.

Leucocytes 9,000/c.mm.

Platelets 252,000/c.mm.

Erythrocyte sedimentation rate 5 mm./1st hr; 12 mm./2nd hr.

Coagulation time – 4 min.

Bleeding time – 2 min.

Blood group – B

Liver function tests were also performed, and found to be within normal limits.

X rays of the skull and orbits were negative.

TREATMENT

The patient was treated for her anaemia, by massive iron preparations, until the blood count reached normal limits. Vitamin C was also prescribed.

FOLLOW-UP

Repeated fundus, slit-lamp, and blood examinations were made for a period of 4 months.

Discussion

The fact that the bleeding was cyclic is evidence of vicarious menstruation. The intercyclic bleeding could be explained by anaemia, which was evident from the blood examination. After we had treated the anaemia, the intercyclic bleeding diminished although the cyclic bleeding was not affected.

Vicarious menstruation has been described as occurring from many sources: the nose, conjunctiva, retina, eyelids, ears, stomach, intestines, rectum, lungs, kidneys, umbilicus, abdominal fistulae, nipples, gums, lips, and skin (Israel, 1961; Novak and Jones, 1961; Duke-Elder, 1965). It usually coincides with normal menstruation, and is supplementary; but if it replaces the normal menstruation, it is substitutional, and occurs sometimes after hysterectomy (Jeffcoate, 1967).

The cause of such bleeding is unknown. Some instances may be explained by a local vascular disturbance, possibly due to oestrogen, while in other cases the blood may issue from benign metastases of the endometrium to bizarre locations (Israel, 1961).

Duke-Elder (1965) reported that vicarious menstruation from the conjunctiva may be due to "instability of the nervous system" and not to a hormonal disturbance. Jeffcoate (1967) mentioned that it was more often found in individuals with "nervous and vascular instability", a fact that was confirmed in our patient.

The commonest form of vicarious bleeding is epistaxis, which is a feature of at least 30 per cent. of cases (Roth, 1920). The nasal mucosa is influenced by oestrogen, and becomes congested and swollen during premenstruation, when the amount of oestrogen in the blood is high; or when the hormone is applied directly to the mucosa. This is the basis for the topical use of oestrogen in the treatment of atrophic rhinitis (Mortimer, Wright, Bachman, and Collip, 1936).

Bean (1953) mentioned that the effect of oestrogen on the capillaries and venules of the skin may account for the rare form of supplementary vicarious menstruation, known as "dermatosis dysmenorrheica symmetrica of Polland". The cause may be a generalized vasospasm with increased capillary permeability during the 2 premenstrual days (Brewer, 1938). This capillary permeability may be produced by menstrual toxin (Macht, 1949; Smith, 1950).

Vicarious menstruation of endometriosis, may arise from pieces of endometrium implanted into the incision during operations on the uterus. This accounts for cyclic bleeding from scar tissue, which occurs in response to ovarian oestrogen from a pinhole opening in the scar (Israel, 1961). It may also arise from a blood- and lymph-borne metastasis of endometrium (Javert, 1951), thus accounting for vicarious menstruation from unusual sites as the kidney (Marshall, 1943).

The first principle of treatment is to make a complete systemic survey to exclude blood dyscrasia and organic lesions. The administration of vitamin K, C, or P, which are designed to strengthen the capillary walls, should be tried (Israel, 1961).

Jeffcoate (1967), advised that "no special treatment is necessary, unless the bleeding is marked and uncontrollable, as when retinal haemorrhages threaten sight; suppression of ovarian function may be considered." A temporary remission can be obtained by administering testosterone.

Summary

A case of vicarious menstruation from the conjunctiva in an anaemic and nervous patient is reported; the bleeding was cyclic in conjunction with the menstrual cycle. Intercyclic bleeding was improved by treating the patient's anaemia.

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Retinoblastoma treated by freezing

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The effect of cryotherapy on intraocular neoplasms is disappointing, except in the case of retinoblastoma, which is readily destroyed by freezing and in which cures have been reported by Lincoff, Maclean, and Long (1967) and Rubin (1969). This communication reports the effect of cryotherapy on the second eye in a case of bilateral retinoblastoma, in which complete histological examination of the treated eye by serial sections was carried out after death, which was caused by metastases from the grossly involved first eye.

Case report

A 3-year-old boy of Cape Coloured descent underwent enucleation of a blind staphylomatous left eye on January 16, 1970.

At this time the right fundus was normal on indirect ophthalmoscopy and he was discharged from hospital 3 days later to be followed-up as an outpatient. Routine histological examination of the enucleated eye revealed a tumour filling the globe and extending into the cut end of the optic nerve stump. The child did not return to the clinic, and after letters had produced no result the police took a message to the family and the child was readmitted on March 1, 1970, which was 6 weeks after the enucleation.

Examination on second admission

The left socket was healthy and no mass could be detected by digital examination. General examination revealed a cheerful well-nourished child.

The right eye showed a large mass of tumour in the superior and superotemporal areas of the fundus with obvious vitreous seedlings (Figs 1 and 2, opposite).

Special investigation

X ray examination of the whole skeleton including the optic foraminae and the lung fields showed no abnormality, and the haemoglobin level, white cell count, and erythrocyte sedimentation rate were all within normal limits.

Therapeutic possibilities

Great reluctance was felt at removing the second eye, particularly as the spread of the tumour from the first eye rendered the prognosis as to life very poor.

The tumour seedlings were too anterior and extended too far into the vitreous for the technique of applying radioactive sources to the sclera to be used (Stallard, 1948). We therefore considered the heroic manoeuvre of inserting a radioactive tantalum wire into the vitreous near the tumour, but planning for this treatment showed that it was impossible to deliver the 10,000 r needed to destroy anoxic vitreous seedlings without causing a cataract, so this approach was abandoned.

Intra-arterial cytostatic agents would only have reached the vitreous seedlings if given in large doses which would cause blindness from retinal fibrosis.

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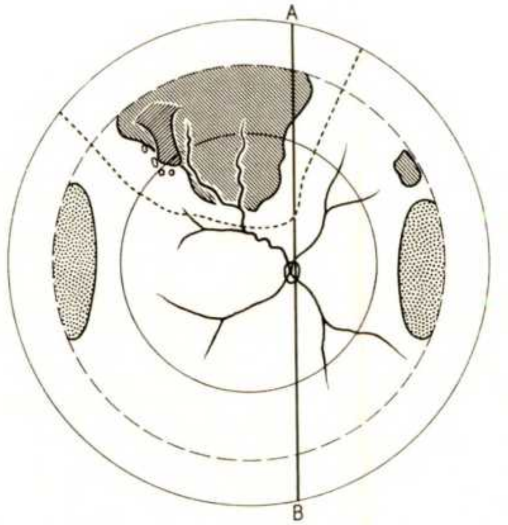


FIG. 1 *Plan of fundus, showing retinoblastoma (hatched), area frozen (outlined - - - - -), and areas removed to allow entry to fixative (dotted)*

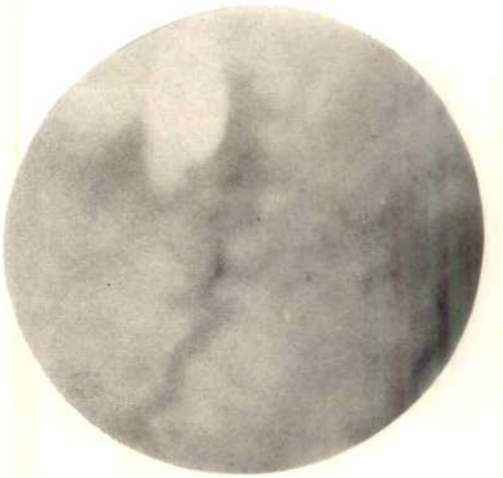


FIG. 2 *Fundus photograph, showing tumour deposits in vitreous*

The only form of local therapy available therefore was to freeze the whole tumour including the vitreous seedlings. This entailed the freezing of about one-fifth of the whole volume of the eye and required an iceball of at least 6 mm. radius in order to include all the tumour deposits in the vitreous. Moreover, this volume of freezing had to be produced without repeated cycles of freezing and thawing in order to avoid severe haemorrhage.

Fortunately a suitable crypoexy machine was available. Originally designed for retinal detachment work and for use with CO_2 gas as a refrigerant, this machine had a 4·5 mm. diameter probe which fell to a temperature of $-86°$C. and could form an iceball 10 mm. in diameter, when liquid nitrous oxide from an anaesthetic gas cylinder was used as the refrigerant (Molteno & Luntz, 1968).

Treatment

Irradiation of both orbits, optic nerves, and chiasmata was started, supplemented by intramuscular triethyl melamine (TEM) and preceeded by cryotherapy to the lesion of the right eye (Fig. 3).

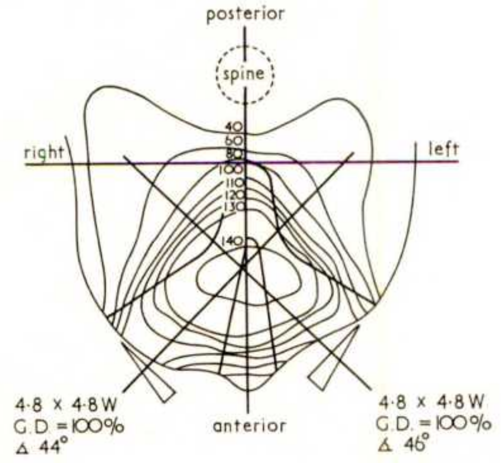


FIG. 3 *Radiotherapy plan, showing equal irradiation of both orbits*

FREEZING TECHNIQUE

Under general anaesthesia the upper half of the globe was exposed *via* an incision in the superior fornix. The probe was applied to the full-thickness sclera. It was positioned by observing indentation with a direct ophthalmoscope and then cooled until the iceball ceased to grow after between 2 and 2½ minutes.

A total of five overlapping applications was given; after this procedure there was considerable vitreous haze in the vicinity of the tumour through which small haemorrhages were visible, but the appearance of the tumour was otherwise unaltered.

POSTOPERATIVE COURSE

For the first week there was considerable conjunctival chemosis and the child could not bear close examination, but 8 days after the operation adequate examination of the fundus was possible. This showed clear media and a greatly shrunken tumour with numerous small discrete haemorrhages on its surface. By the 14th day most of the tumour had disappeared to leave a finely pigmented choroido-retinal scar. A yellow area of thickened retina some four disc diameters across and situated three disc diameters above the disc together with a small cluster of vitreous seedlings (which included the tip of the stalactite like deposit shown in Fig. 2) remained.

Re-operation

3 weeks after the first operation the residual tumour was treated by freezing. The superior rectus muscle was detached to allow access to the mass near the disc, while the area frozen was extended forward to include part of the ciliary body and any tumour deposits hidden amongst its processes. By indenting the sclera more deeply, the iceball was increased to include the remaining vitreous seedlings. Eleven overlapping applications were given, taking care to avoid freezing any area of tissue more than three times by slightly offsetting adjacent rows of applications.

POSTOPERATIVE COURSE

The residual tumour again showed scattered small haemorrhages during the first week but by the end of the second week all signs of tumour had disappeared, leaving an oval pupil displaced superotemporally, a localized equatorial lens opacity, a large area of fine pigmentary disturbance in the fundus, and macular oedema which resolved during the third week after operation.

The child appeared to see well, played normally, and continued to receive cobalt^{60} radiation (supplemented by three doses of 0·97 mg. intramuscular TEM) to a total dosage of 3,510 r.

Appearance of metastases

On May 3, 1970, a mass developed in the left socket to be followed shortly by widespread bony metastases and irregular enlargement of the liver. All active treatment was discontinued apart from opiates used to control pain. The metastases enlarged rapidly until death ensued on July 15, 1970.

The child could see and grasp accurately small objects offered to him 3 days before death. Immediately after death the fundus was examined by direct ophthalmoscopy and showed clear media with no signs of tumour. The eye was then enucleated, injected with buffered glutaraldehyde formalin solution, and placed in a container of the same fixative.

Autopsy findings

Both orbits and their contents were removed and the incratranial portions of both optic nerves and the chiasma were examined histologically at sixteen different levels.

The final diagnosis was that of a poorly differentiated fungating retinoblastoma of the left orbit with infiltration of all orbital structures. Spread into the subarachnoid space adjacent to the optic chiasma had occurred, with widespread metastases to the skeleton (including the calvaria, rib cage, vertebral bodies, and right femoral neck, para-aortic lymph chain, liver, pancreas, and suprarenal bodies.

LEFT EYE

The histological appearance of the left eye, the left orbital recurrence, and all the secondary deposits examined was similar: an ill-differentiated tumour made up of medium-sized cells with deeply staining basophilic nuclei, and scanty cytoplasm; approximately six mitotic figures were present in each high-power field; areas of necrosis were present in the larger deposits but true rosette formation was not seen. Sections through the intracranial portions of the optic nerves and chiasma showed tumour cells in the subarachnoid space next to the left optic nerve and the left side of the chiasma, but the nerve tissue itself was not invaded.

RIGHT EYE

After fixation the eye was opened by cutting small windows just posterior to the insertions of the medial and lateral rectus muscles to allow entry of the paraffin wax.

After imbedding, the eye was cut into serial sections; these were stained with haematoxylin and eosin, except for every 50th section for which Verhoeff's connective tissue stain was used. The sections (715 in all) were examined under ×25 and ×250 magnification. An oil immersion lens with ×1,000 magnification was used to examine areas of special interest.

Histological findings

The frozen area showed marked thinning of retina and choroid and atrophy of the ciliary body and iris. The extent of these changes was measured on every 50th slide in order to construct the diagram (Fig. 1). The section along the plane A–B is shown in Fig. 4.

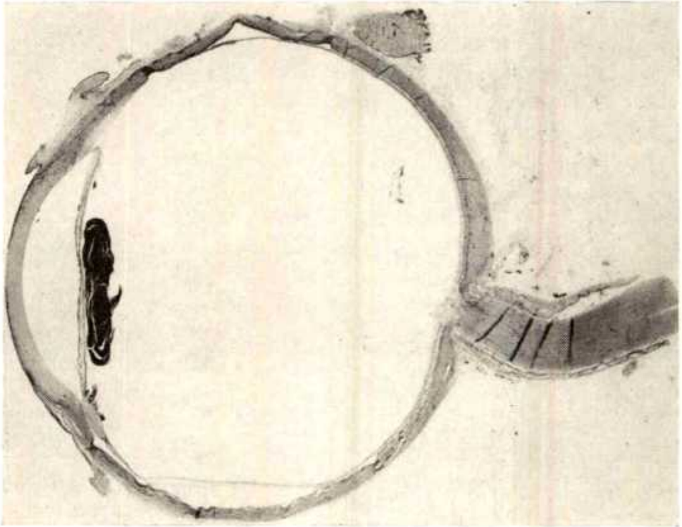
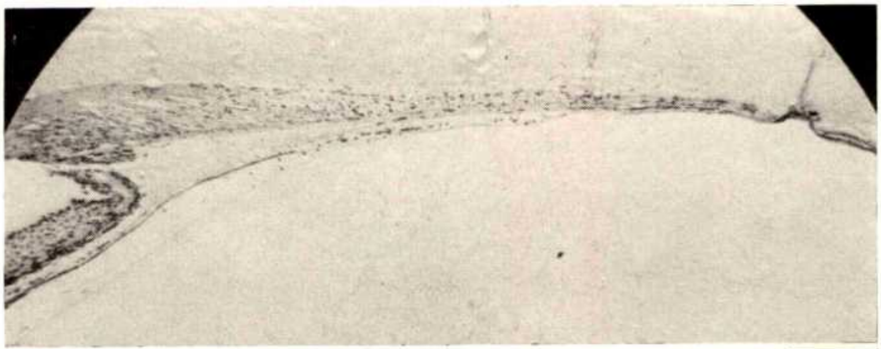


FIG. 4 *Section along plane A-B of Fig.* 1, *showing effects of freezing on iris, ciliary body, and retina extending posteriorly to a point* 4 *disc diameters above the optic nerve. Haematoxylin and eosin.* ×1·6

The vitreous formerly occupied by tumour tissue showed fine eosinophilic fibrils irregularly and loosely arranged with a total absence of cellular elements (Figs 5 and 6, overleaf).

The retina and choroid layers were fused together with loss of rod and cone outer segments and of ganglion cell nuclei at the periphery of the frozen area, but centrally the retina was markedly thinned and reduced to a feltwork of glial fibres containing a few nuclei resembling those of fibroblasts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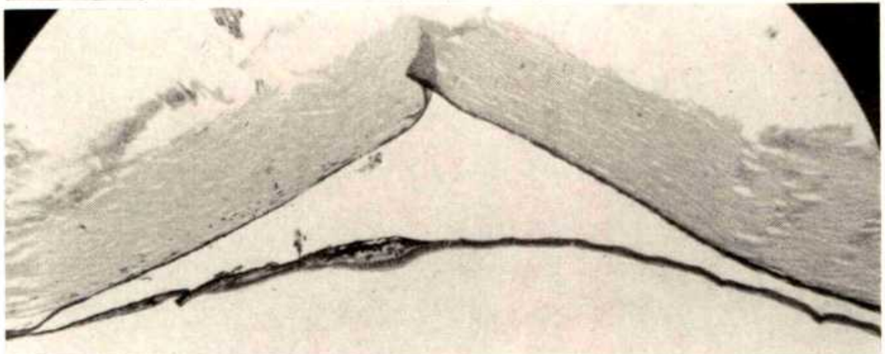
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FIG. 5 *Higher-power view of Fig. 4, showing changes in iris, ciliary body, and adjacent vitreous. Haematoxylin and eosin.* ×18

FIG. 6 *Higher-power view of Fig. 4, showing changes in peripheral retina and adjacent vitreous. Haematoxylin and eosin.* × 18

together with scattered uveal and neuroepithelial pigment containing cells. The retina in these areas was firmly fused with pigment epithelium which was irregularly thickened.

The choroid showed marked thinning with disappearance of the choriocapillaris and many of the medium-sized blood vessels. Bruch's membrane was not prominent in any of the sections, but the artefactual separation of the pigment epithelial layer from choroid around the periphery of the frozen areas demonstrated that it was probably intact, while more centrally, where it had been maximally frozen and where tumour tissue had been situated, the presence of uveal pigment-containing cells in the retina demonstrated that it had been breached either by excessive freezing or by the tumour (Figs 4 to 9, above and opposite).

The iris and ciliary body showed marked stromal atrophy and complete disappearance of the neuroepithelial layers where frozen (Fig. 5).

In the lens the localized equatorial opacity noted during life could not be detected histologically.

The remainder of the eye which had not been treated by freezing showed histologically normal retina, fovea, choroid, ciliary body, iris, drainage pathways, and optic nerve, with the exception of a minute area of retinoblastoma situated nasally and quite separate from the treated area. This retinoblastoma *in situ*, which showed typical histological features of the tumour, appeared to be originating from the inner nuclear layer and was confined to the retina except for three minute vitreous seedlings.

The only unusual findings were an almost complete lack of mitotic figures (1 to 8 per section), vacuolation, and hyperchromicity of nuclei in certain areas. These changes, probably caused by radiotherapy and TEM, were interspersed with areas of morphologically normal tumour cells; there was nothing to suggest that necrosis or shrinkage of the tumour had occurred (Figs 10 and 11, overleaf).

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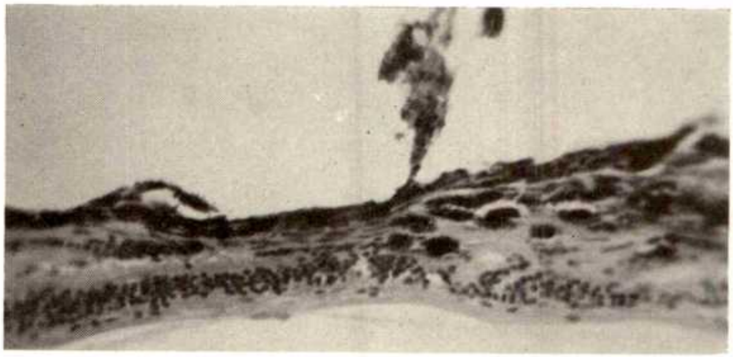


FIG. 7 *Centre of frozen area, showing fusion of retina and choroid with destruction of normal architecture but no recognizable tumour. Haematoxylin and eosin.* × 190

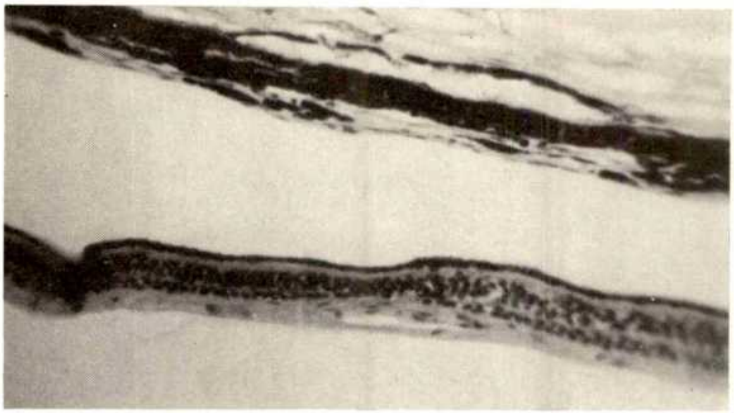


FIG. 8 *Heavily frozen area not involved by tumour, showing loss of rod and cone outer segments and of ganglion cells, but retention of traces of normal architecture. Haematoxylin and eosin.* × 190

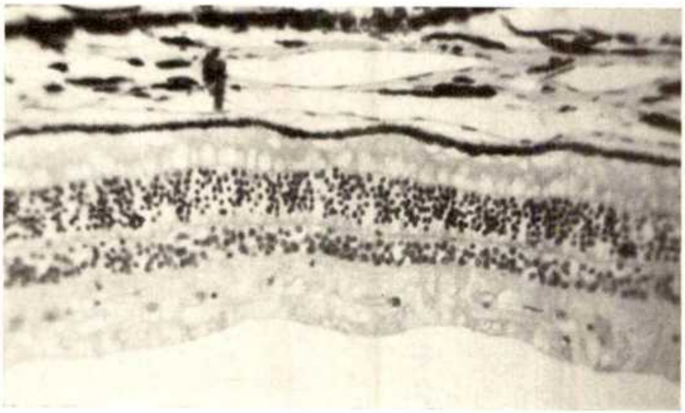


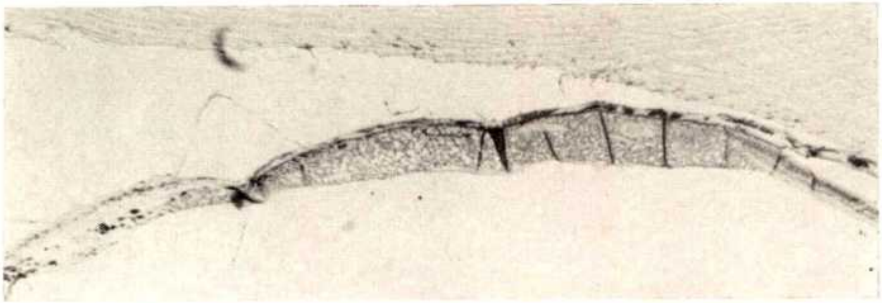
FIG. 9 *Posterior margin of frozen area, showing minimal changes: loss of ganglion cells and damage to rod and cone layer which is fused to pigment epithelium. Haematoxylin and eosin.* × 190

Discussion

The tumour in this case was of the anaplastic type and behaved aggressively, spreading rapidly and widely, but did not secrete significant amounts of vanillyl mandilic acid even when metastases had become clinically obvious.

The tumours of the right eye were almost certainly independent primaries, as the first appeared 3 months before any other secondaries, and the second was confined to the peripheral retina – a most unusual site for a blood-borne tumour metastasis.

The persistence of apparently viable tumour in the right eye (10 weeks after completion of a full course of Cobalt^{60} and TEM therapy), the massive early recurrence in the left



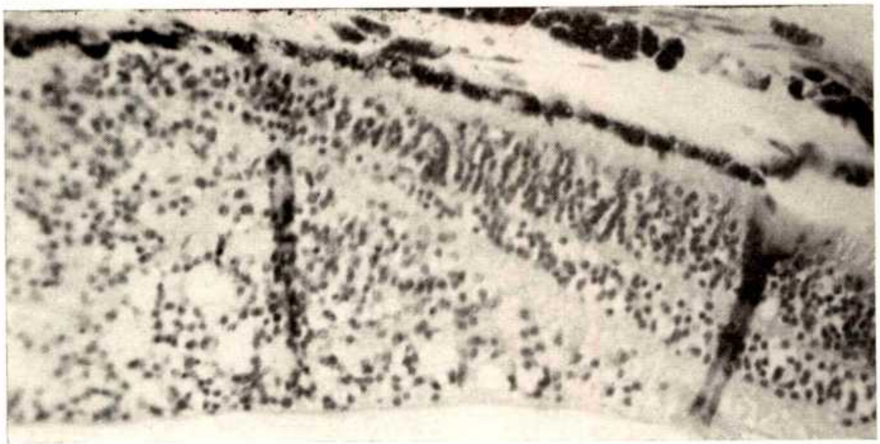


FIG. 10 *Retinoblastoma* in situ. *Haematoxylin and eosin.* ×18

FIG. 11 *Margin of retinoblastoma* in situ, *showing origin from inner retinal layers. Haematoxylin and eosin.* ×375

orbit, and the clinical behaviour of the frozen tumour strongly suggest that cryotherapy was the only effective therapeutic agent in this case.

Summary

(**1**) A case of bilateral retinoblastoma is described, together with the techniques used to freeze the tumour tissue in the second eye.

(**2**) The autopsy findings are reported, including the histological examination of the treated eye by means of serial sections.

The authors wish to thank Dr. A. B. W. Ferreira, Prof. C. J. B. Muller, and Prof. H. W. Weber, Heads of the Departments of Ophthalmology, Radiology, and Pathology, for their support, Mr. R. S. Schmidt Senior Technician who cut the sections, and to the Department of Medical Illustration of the University of Stellenbosch.

Our thanks are also due to the Superintendent of Karl Bremer Hospital for permission to publish this case.

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Correspondence

Operations on the eyes of Africans

To the Editorial Committee of the **British Journal of Ophthalmology**

SIRS,—Concerning the article "Failure of Filtering Operations in the African" by N. H. Welsh (*British Journal of Ophthalmology*, 1970, **54**, 594), I should like to bring to your attention our publication, Excision of Tenon's Capsule in Fistulizing Operation on Africans. With this technique we obtained success rates of more than 90 per cent., and it became clear that Tenon's capsule excision prevented scarring and closing of the bleb.

It should become the operation of choice in Africans. Subsequent experience in many patients and further follow-up of the group originally described confirmed our results.

DEPARTMENT OF OPHTHALMOLOGY,
HADASSAH MEDICAL ORGANIZATION,
JERUSALEM,
ISRAEL

Yours faithfully,
I. BEN-SIRA

March, 4 1971

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BEN-SIRA, I., and TICHO, U. (1969) *Amer. J. Ophthal.*, **68**, 336

Book reviews

Physiology of Colour and Pattern Vision. By K. MOTOKAWA. 1970. Pp. 283, 137 figs. Igaku Shoin, Tokyo; Springer, Berlin. (DM 72; U.S. $18.)

This book describes and discusses the long series of researches on the visual process carried out in the last 25 years by Motokawa and his co-workers in Japan. The work falls broadly into two categories: electrophysiological, including the discovery of the so-called X-component of the electroretinogram, and psychophysical, concerned mainly with the observations and implications of the effects of pre-exposed light stimuli on the electrical phosphene. It is this latter work – particularly with Motokawa's name – that has sometimes puzzled vision researchers in the West, and which seems to have remained separated from the main stream of development in visual science. No doubt partly responsible for this situation are two facts. Firstly, the basic initial papers appeared in the aftermath of the war, often in less easily accessible Japanese journals and, secondly, phosphene measurements of the Motokawa type involve a difficult technique and would appear to need (for success) suitable trained subjects. The present book is particularly welcome as providing an authoritative, coherent, and well-written account of the whole development, covering details of the method, the principal experimental studies, and the extensive superstructure of deduction and theory erected on the results obtained.

When a single brief electric pulse is passed through the retina, *via* electrodes applied to the forehead, the minimal current needed to produce a luminous repsonse (phosphene) defines the electrical threshold, and its reciprocal, the electrical excitability. In 1949, Motokawa showed that excitability was increased if a light stimulus were applied to the retina at any time in the period from about 0·5 to 10 sec. before the pulse. He introduced the quantity

$$\zeta = [(E - E_0)/E_0]\ 100$$

as a measure of the "physiological effect" of the light stimulus, where E_0 is the excitability of the dark-adapted retina in its resting state, and E is the excitability at a particular moment after a specified pre-exposure of one (or more) light stimuli. Practically all the psychopyhsical work reported depends on measurements of ζ. A few examples of the very many results obtained may be quoted. After a brief monochromatic stimulus, the shape of the curve of ζ against time is characteristic only of the wavelength of the stimulus, an increase in its intensity merely having the effect of raising the whole curve. If the stimulus is applied at the fovea, the time course shows a maximum value of ζ at a time increasing from 1 to 3 sec. as the wavelength moves from red to blue, while for violet stimuli there are two peaks, at 1 and 3 sec. For peripheral stimuli of sufficiently low intensity, all wavelengths give a single peak occurring at the same time (2 sec.). By these and other experiments with single monochromatic stimuli, Motokawa is able to derive so-called "physiological sensation curves" attributed to the rod system for peripheral stimuli and to 'red', 'green', and 'blue' cone systems for foveal stimuli. While his derivations are not always as rigorous as could be desired, the curves so obtained resemble spectral sensitivity curves for rod and cone systems arrived at by entirely different methods. When more than one light stimulus is used, the scope of Motokawa's method is extended to inductive effects. If a coloured stimulus is applied a second or two before a white stimulus and on the same retinal area, the white only ζ-time curve is raised and its peak time is displaced in a way depending on the colour (direct induction, correlate of successive contrast). If the coloured stimulus is applied in an area adjoining that of the white, similar effects are observed, except that the modifications of the ζ-time curve are those which would be produced by direct induction using a stimulus of the complementary colour (indirect induction, correlate of simultaneous contrast.) The indirect induction produced by one coloured stimulus can be neutralized by the indirect induction of a (third) stimulus of the same colour. Also the indirect inductive effects of two coloured stimuli can cancel out if their colours are complementary. In further work, still more elaborate spatial and temporal distributions of pre-exposed stimuli are used – the measured quantity being always ζ – and Motokawa reaches the general conclusion that the inductive effect of a light stimulus has many of the properties of a wave propagation over the retina. He determines the velocity of propagation and demonstrates reflection (a supplementary white bar stimulus both blocks the spreading induction and re-directs it as a reflected wave), refraction, diffraction, and Doppler effect. In another group of experiments, the inductive field round the figures of familiar optical illusions (*e.g.*, the Müller-Lyer figure) was measured and plotted as a contour of constant ζ value. From the characteristics of such diagrams, explanations, or at least interpretations, of the illusions are derived. When the single electric pulse for generating phosphenes is replaced by alternating current stimuli of various frequencies, the action of pre-exposed monochromatic light stimuli is shown to be most pronounced at certain 'resonance' points where the wavelength of the light and the frequency of the alternating current stand in a special relation. These resonances are associated with different receptor mechanisms in the retina, of which Motokawa identifies three in the fovea and four in the periphery, in addition to a resonance produced by the rod system.

Unfortunately, little work on phosphenes on the lines of Motokawa's has been done outside the laboratories of his school. Riggs, Cornsweet, and Lewis (1957) observed the enhancement of excitability by a pre-exposed light stimulus but could not confirm the wavelength dependence of the effect. This is attributed by Motokawa to their use of an inappropriate measuring technique. Whatever reservations may be felt about Motokawa's data and his inferences from them, there is no doubt that further independent checks on the salient results should be made.

In the objective electrophysiology – the electroretinogram, slow potentials, and spike activity, lateral geniculate and cortical response, receptive fields, etc. – which occupies the first three of the eleven chapters of the book, the author's researches dovetail with much current work, and he gives an interesting and detailed review of the present situation as he sees it.

In all, this is a book that every library concerned with the visual sciences will need to have.

Postoperative Disturbances of Wound Healing. (Postoperative Wundheilungsstörungen.) Edited by F. W. GIERHAKE. 1970. Pp. 74, 15 figs. Springer, Berlin. (DM 19.80.)

In this stimulating work, the authors deal with disturbances of primary wound healing from both bacterial and other more mysterious causes. When accurate records of careful observations are analysed they find an overall figure of 10 to 15 per cent. abnormality in healing. It is most important to rely on careful statistics and not estimates and subjective impressions, and the examination of records of over 30,000 general operations cover series both before and after the second world war. The incidence of complications shows no change despite the introduction of antibiotics which may indeed have led to less strict asepsis in surgery. The role of bacteria and antibiotics is detailed and other factors are considered. The age of the patient and acuteness of the condition concerned are important; time of year is not. Figures vary with the nature of the operation but the statistics for different series of the same operation are consistent. Although the patient's age and the duration of the operation are two factors which have worsened recently, improved anaesthesia and earlier mobility have countered them. The references and index are good and the editor's observations on the principles of sound wound healing, and especially his insistence on the need for continued asepsis, will apply to ophthalmic surgery as much as to the general surgery he considers.

Physiological Bases of Light and Colour Sensations. (Physiologische Grundlagen der Helligkeits-fund Farbempfindungen.) By W. STARKIEWICZ. 1970. Pp. 128, 41 figs, 81 refs. Ophthalmological Monographs No. 39. Thieme, Leipzig. (D.M. 37.)

The author surveys the physiology of vision and the relation of the physiological data to the perception of light and colour. He believes that only under unusual conditions are the perceptions strictly related to the stimulus and the physiological processes in the retina and the optic pathways. Under normal familiar circumstances, the impressions are modified by psychical adaptation, especially by verbal associations mediated from Broca's centre. The author calls this auditory cooperation a "verbal reflex". It appears difficult to distinguish between normal and unusual circumstances. Further, the reviewer calls as witness Duke-Elder who stated that "the vision of colour in normal illumination is no less problematic than vision in abnormal illumination". The combination with tactile impression, which the author recommends for the re-education of a faulty localization after squint operations, has been practised for a long time. The statements that psychological adaptation can succeed in perceiving as upright an image which has been inverted by a "prism" and that a nervous impulse is travelling up to a "meningeal" centre are obvious mistakes. The author believes in the generally accepted three-cone colour theory of Young-Helmholtz. The explanation offered by this theory for the phenomenon of simultaneous and successive contrast, and that of complementary-coloured after-images is not very convincing, though it has to be admitted that Hering's teaching of dissimilation and assimilation is also open to criticism. The old conception that different sense perceptions have to make use of different nerve fibres is controversial. since it has been demonstrated that elements in the optic nerve and in the lateral geniculate body react differently to an "on" stimulus of light waves than to an "off" stimulus. It is conceivable that the same cone reacts in eliciting a different colour sensation by different wavelengths of light. Hitherto even the electron microscope has shown no anatomical difference between the cones which are supposed to react independently on red, green, or blue light waves. The author describes with remarkable certainty, the electrical processes in the bipolars and higher up to the red, green, and blue cortical centres. This is illustrated by schematical pictures.

An appendix describes an electric "eye", consisting of photo-electric cells, which transmit optic stimuli to levers acting on the skin. These tactile impressions should enable a blind man to avoid obstacles when walking.

Physiology of the Retina and Visual Pathway. By G. S. BRINDLEY. 2nd ed., 1970. Pp. 315, illus., bibl. Arnold, London (Monographs of the Physiological Society, No. 6). (£4·50)

The second edition of Professor Brindley's book is an important event. There have been enormous advances in visual research in the last 10 years, many of which are incorporated in this monograph. Half of the book is devoted to physiology and half to visual psychophysics.

The new material deals mainly with photochemistry, the early receptor potential, and intracellular records from retinal cells. The central pathways of vision are treated somewhat sketchily. The most important work on the visual cortex (by Hubel and Weisel) is given three pages; the same allocation as is made elsewhere to interesting but inconclusive work on electrical phosphenes. There is little treatment of recent developments in experimental neuroanatomy, and no mention of the psychophysics of binocular vision. Thus, as is admitted in the introduction, the coverage is idiosyncratic, but what is dealt with has authority and distinction.

Stereoscopic Atlas of Slit-lamp Biomicroscopy. Vols I and II. By A. E. BRALEY, R. C. WATZKE, L. ALLEN, and O. FRAZIER. 1970. Pp. 225, 213 figs, 210 stereoscopic views in colour on 30 reels. Mosby, St. Louis; Kimpton, London. (£35·75)

This atlas comprises 210 stereoscopic pairs of slides with accompanying text and pictures. There is also a brief introduction describing the techniques used to prepare the slides. The authors claim that, as most features of the eye are viewed stereoscopically, they are best recorded stereoscopically. Several hundred cases seen in the Department of Ophthalmology at the Univeristy of Iowa have been recorded in this way, and the atlas contains a selection of this material to demonstrate either good teaching cases or rare clinical conditions.

The photographs are grouped according to the structure involved; conjunctiva, cornea, iris, anterior chamber, lens, vitreous, and retina and choroid. Within these groups the order of presentation is completely haphazard but this is a minor irritation. Unlike most atlases this volume does not cover the subject comprehensively and certain conditions receive a disproportionately large representation; there are, for example, five views of a pigmented angle. Other common conditions might have been given more space and the treatment of diabetic changes is disappointing. It is always interesting to view a rare condition, but the authors seem to have chosen a poor case of the rapidly disappearing condition of mustard gas keratopathy as they show a non-specific corneal ulcer and do not demonstrate the classical vessel aneurysms on an otherwise avascular sclera.

As far as technical merit is concerned the series is excellent. Either a broad-beam or a slit-beam is used for illumination, and the former gives the more impressive sensation of depth. The slit-beam views of the angle are excellent but those of the fundus are far less informative. Indeed, without the descriptive text, it would be difficult to know what some pictures represent. Certain subjects lend themselves to beautiful portrayal, particularly the various lens opacities. Two pictures leave a particular impression, one a diabetic cataract and the other of a posterior vitreous detachment.

It is difficult to determine who will be best helped by this book. The experienced ophthalmologist will be interested to see a case of angle recession but will not be edified by an illustration of a dendritic ulcer or of an aqueous flare, whereas the undergraduate would be better served by the latter. There is no doubt that the book should be available to every junior ophthalmologist, but whether it should be placed in the library or the museum is up to the purchaser. The production of this text raises possibilities of expansions. For some years pathologists have held meetings at which slides of interesting cases have been exchanged. Of recent years stereoscopic illustrations of interesting cases have been published in the journals but perhaps clinicians could exchange their stereoscopic views with relevant data.

A final practical point is that anyone able to afford this book will be advised to buy a good stereoscopic viewer, the collapsible model supplied is unlikely to survive the hard wear that the illustrations merit.

Notes

International Society of Geographical Ophthalmology

Jerusalem, August 23–24, 1971

The Committee comprises Prof. Ida Mann (*Australia*), Prof. Weigelin (*Bonn*), Dr. J. Holmes (*Hawaii*), Dr. A. Kornzweig (*New York*), Dr. Viggo Clemmensen (*Naestved, Denmark*), Dr. E. E. Cass, S. M., President (*Fort Smith, N.W.T., Canada*).

After the first International Congress of Regional Ophthalmology, held under the presidency of Dr. Gordon Kelly of Toronto, a committee was formed and the Society was renamed the International Society of Geographical Ophthalmology: the membership fee is £10 a year.

The next meeting of the Society will be held at Jerusalem on August 23 and 24, 1971, in conjunction with Prof. I. C. Michaelson's congress on the Causes of Blindness and their prevention in different countries of the world.

It was intended not only for ophthalmologists but also for administrators dealing with the prevention of blindness.

In order to co-ordinate with the prevention of blindness congress, the official themes will be: glaucoma, diabetic retinopathy, cataract, corneal opacification, retinal detachment, and amblyopia.

Papers on any of the above subjects are requested but they must be strictly confined to geographical themes. Précis of papers should be sent as soon as possible to Dr. E. E. Cass, Box 688 Fort Smith, N.W.T., Canada.

II International Symposium on the Lacrimal System

April 22–23, 1972, *Budapest, Hungary*

The symposium will be held in association with the IV Congress of the European Society of Ophthalmology (April 17 to 21, 1972).

Guest lecturers will include: F. Antoni (*Hungary*), Josef Bock (*Austria*), John Charamis (*Greece*), Arnold Forrest (*U.S.A.*), Benjamin Milder (*U.S.A.*), John Clark Mustarde (*Scotland*), A. Neetens (*Belgium*), Magda Radnot (*Hungary*), Salme Vannas (*Finland*), Everett R. Veirs (*U.S.A.*), B. A. Weil (*Argentina*), and A. Werb (*England*).

Further information may be obtained from Everett R. Veirs, M.D., Chairman, Second International Symposium, Scott and White Clinic, Temple, Texas 76501; and from the Secretariat of the IVth Congress of The European Society of Ophthalmology, c/o I Eye Clinic, University Medical School, VIII. Illes u. 15, Budapest, Hungary.

American College of Surgeons

Congress, Atlantic City, October 18–22, 1971

The 57th Annual Clinical Congress of the American College of Surgeons will be held in Atlantic City from October 18 to 22, 1971.

Seventeen postgraduate courses are offered, amongst which is one on Ophthalmic Surgery—Surgery of the Extraocular Muscles.

For further information apply to Mr. T. E. McGinnis, American College of Surgeons, 55 East Erie Street, Chicago, Illinois, 60611, U.S.A.

Bascom Palmer Eye Institute, Miami

Symposium, March 26–31, 1972

A symposium on Ophthalmic and Plastic Surgery will be held under the auspices of the Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami School of Medicine, and the Florida Lions Eye Bank, at the Diplomat Hotel, Maimi Beach, Florida, on March 26 to 31, 1972. Information may be obtained by writing to: Ophthalmic Plastic Surgery Symposium, Bascom Palmer Eye Institute, P.O. Box 875, Biscayne Annex, Miami, Florida 33152.

American Society of Contemporary Ophthalmology

Doctor Jules François, Professor of Ophthalmology at the University of Ghent, was awarded the first Distinguished Service honorary gold medal of the society at the annual meeting in 1971, at Hollywood, Florida.

1972 Winter Meeting, Hollywood, Florida, March, 1972

CALL FOR PAPERS

The 1972 winter meeting of the Society of Contemporary Ophthalmology will be held from February 27 to March 3, 1972, at the Diplomat Hotel, Hollywood, Florida. The Theme of the meeting is "Contemporary Clinical Ophthalmology through Continuing Education".

Lectures will be given by the distinguished permanent faculty. Free time has been made available for ophthalmologists who wish to present papers containing new material on cataract, glaucoma, strabismus, retinal diseases, and all other eye topics. Papers will be selected on the basis of merit, originality, importance, and general interest. Please send title and 150 word abstract, *before October* 1, 1971, to: Dr. John G. Bellows, 30 North Michigan Avenue, Chicago, Ill., 60602, U.S.A.

Keeler Award

The Keeler Award is a Trust established to enable British ophthalmologists to travel anywhere in the world in order to study, assess, and report at first hand, for the benefit of British ophthalmology, on methods on which nothing may yet have been published.

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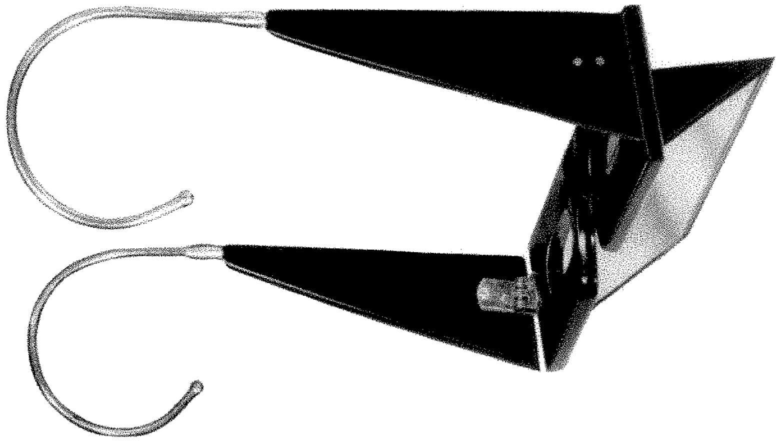

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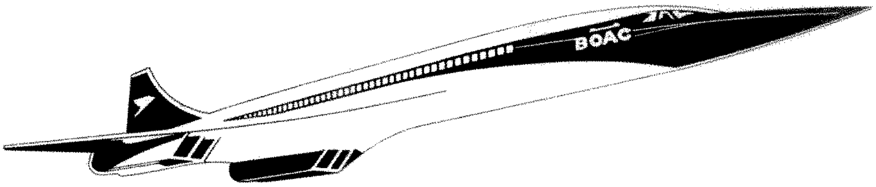

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RECOMMENDED READING IN OPHTHALMOLOGY

TELEVISION OPHTHALMOSCOPY: Instrumentation and Medical Applications *by* **Richard L. Dallow,** *Dept. of Health, Education and Welfare, Washington. Foreword by* **Cesar A. Caceres.** Brings together information from the fields of ophthalmology, optics, photography, television, and electronic analysis for an understanding of the system and opportunities for its application. The capabilities and limitations of television for examining the human ocular fundus clinically are considered and compared with other standard methods of ophthalmoscopy. '70, 120 *pp.* (6¾ × 9¾), 42 *il.*, 1 *table*, $8.50

EYE INJURIES *by* **Edward Zagora,** *Univ. of Sherbrooke, Canada.* Discusses incidence, etiology, pathology, diagnosis, prognosis, prophylaxis, and treatment for most conditions. Chapters on posttraumatic plastic surgery are presented as a compilation of operations which have proven to be successful in the authors' hands. Substantially concerned with ocular symptoms associated with neurological and neurosurgical conditions due to trauma. Clinical photographs, fundus photographs, drawings, diagrams, and tables supply abundant illustrative material to supplement the text. '70, 618 *pp.* (7 × 10), 375 *il.*, 4 *tables*, $30.75

CORNEAL AND EXTERNAL DISEASES OF THE EYE: First Inter-American Symposium *compiled and edited by* **Frank M. Polack,** *Univ. of Florida, Gainesville.* (54 *Contributors*) Covers diagnosis and treatment of bacterial, viral and fungal infections of the cornea, parasitic infections of the eye and its treatment, up-to-date status of epikeratoprosthesis and soft contact lenses in the treatment of corneal diseases, keratoprosthesis—its scope, techniques, and complications, problems in corneal grafting, and microsurgery. '70, 400 pp. (6¾ × 9¾), 217 *il.* (2 *in full color*), 46 *tables*, $24.00

CONTACT LENS MEDICAL SEMINAR: Volume I. Proceedings of the First Biennial Contact Lens Medical Seminar Held in Conjunction with the Annual Meeting of the American Academy of Ophthalmology and Otolaryngology. *Edited by* **Whitney G. Sampson** *and* **Gerald L. Feldman.** *Foreword by* **Joseph M. Dixon.** *Introduction by* **Abraham Schlossman.** (10 *Contributors*) Covers fundamentals as well as clinical applications of corneal physiology, control and management of optical problems, selected fitting problems, and scleral lenses. Emphasis is on adapting basic procedures to office practice. '70, 192 *pp.*, 31 *il.*, 17 *tables*, $10.50

SO YOU HAVE CATARACTS: What You and Your Family Should Know *by* **Albert E. Sloane,** *Harvard Medical School, Boston.* To save time for the physician by answering often-asked questions by the patient, and motivate the patient to continue treatment. Includes a narrative sequence of the natural history of a cataract from onset until after surgery and its correction with glasses or contact lenses. "Hundreds of ophthalmologists and thousands of patients will have cause to rise up and bless the name of Dr. Sloane for this useful book"—Archives of Ophthalmology. '70, 106 *pp.*, 5 *il.*, $5.75

Symposium on OCULAR ANTI-INFLAMMATORY THERAPY *edited by* **Herbert E. Kaufman,** *Univ. of Florida, Gainesville.* (38 *Contributors*) Synthesizes both new and previously published data into a complete analysis of this problem. Discusses efficacy of therapy for different types of diseases and complications, uses of anti-inflammatory agents in treating several types of infection, problem of corticosteroid therapy and glaucoma, and clinical and laboratory methods of assaying and comparing both the efficacy and toxicity of anti-inflammatory agents. '70, 290 *pp.* (6¾ × 9¾), 80 *il.* (23 in full color), 66 *tables*, $19.00

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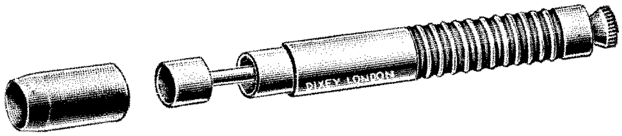

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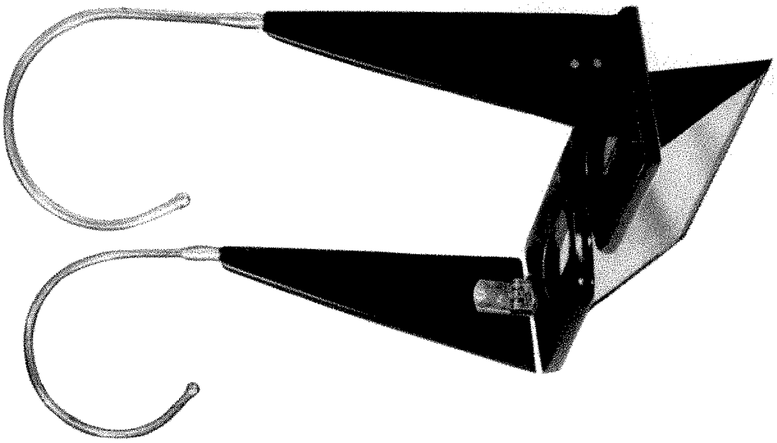

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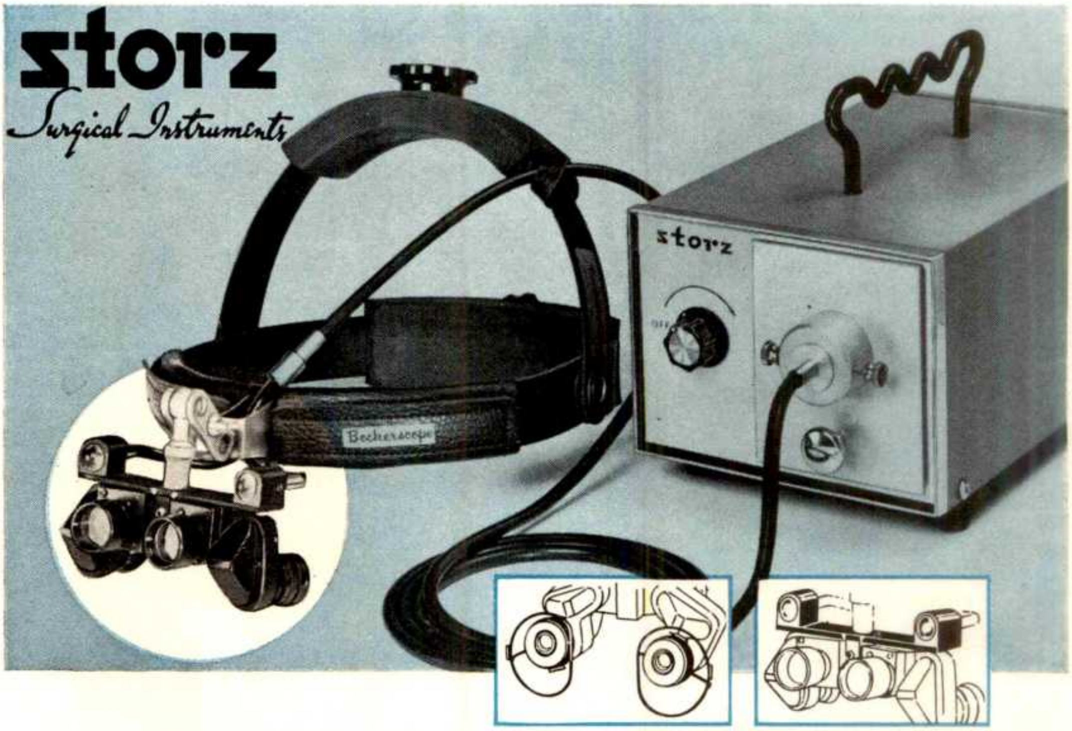

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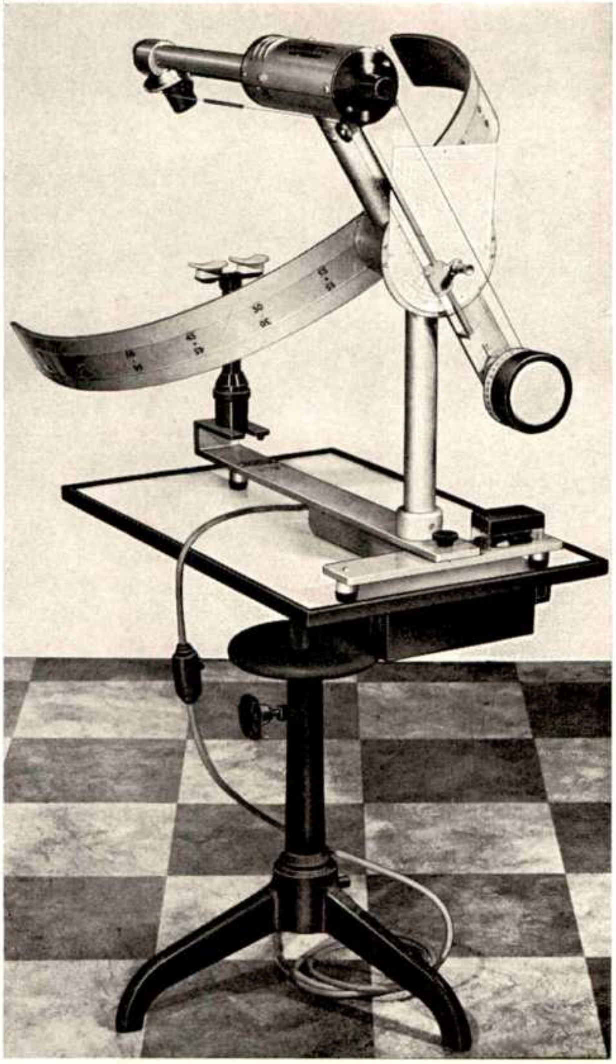

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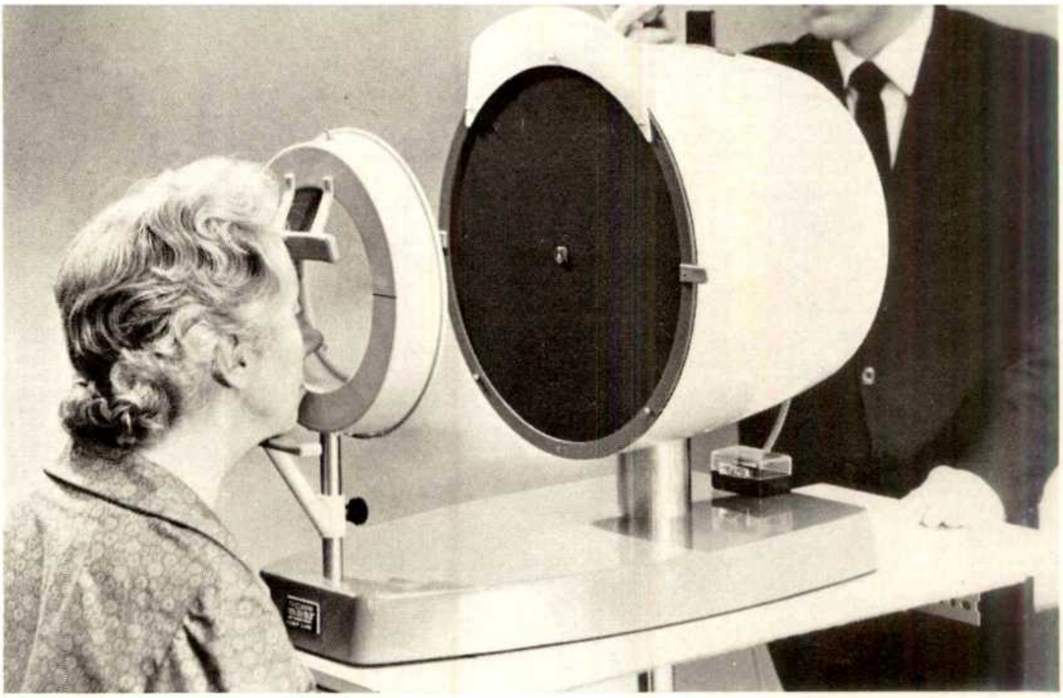

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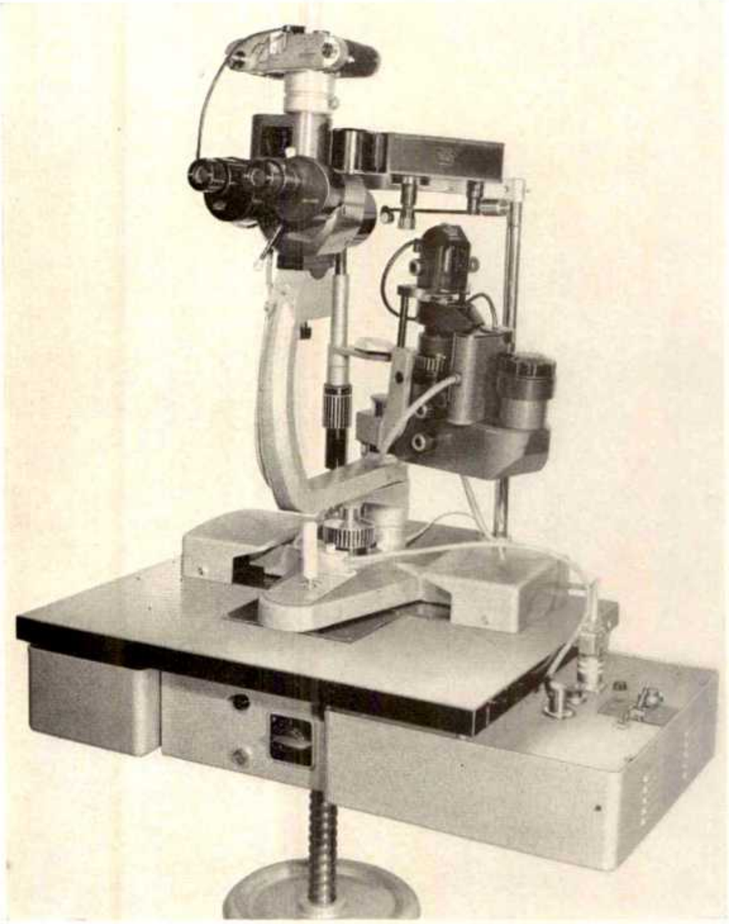

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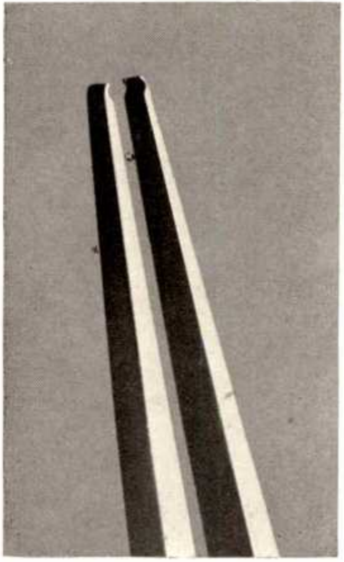

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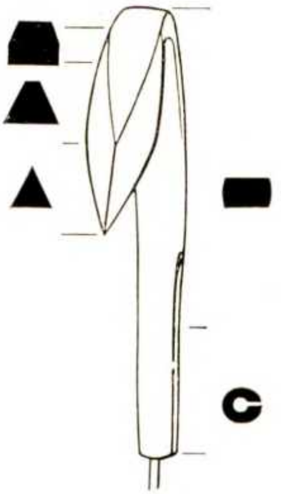

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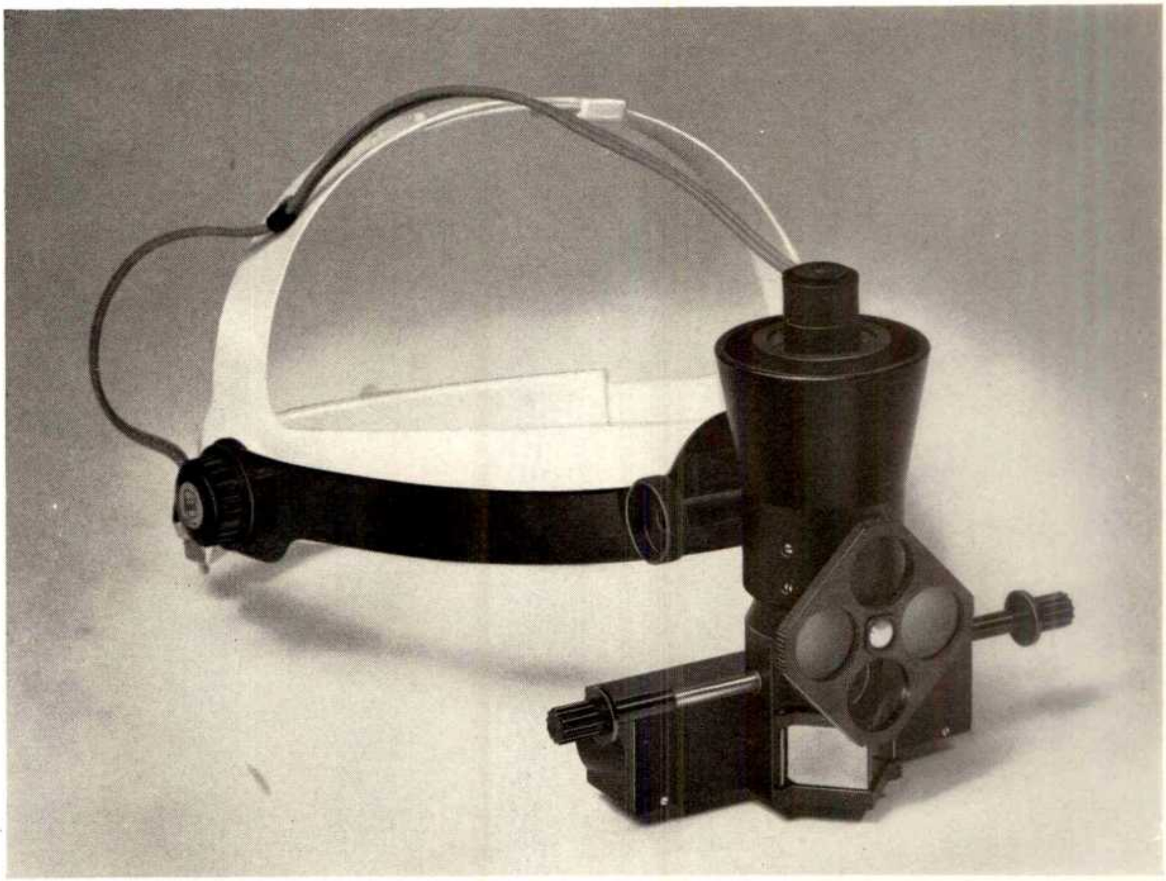

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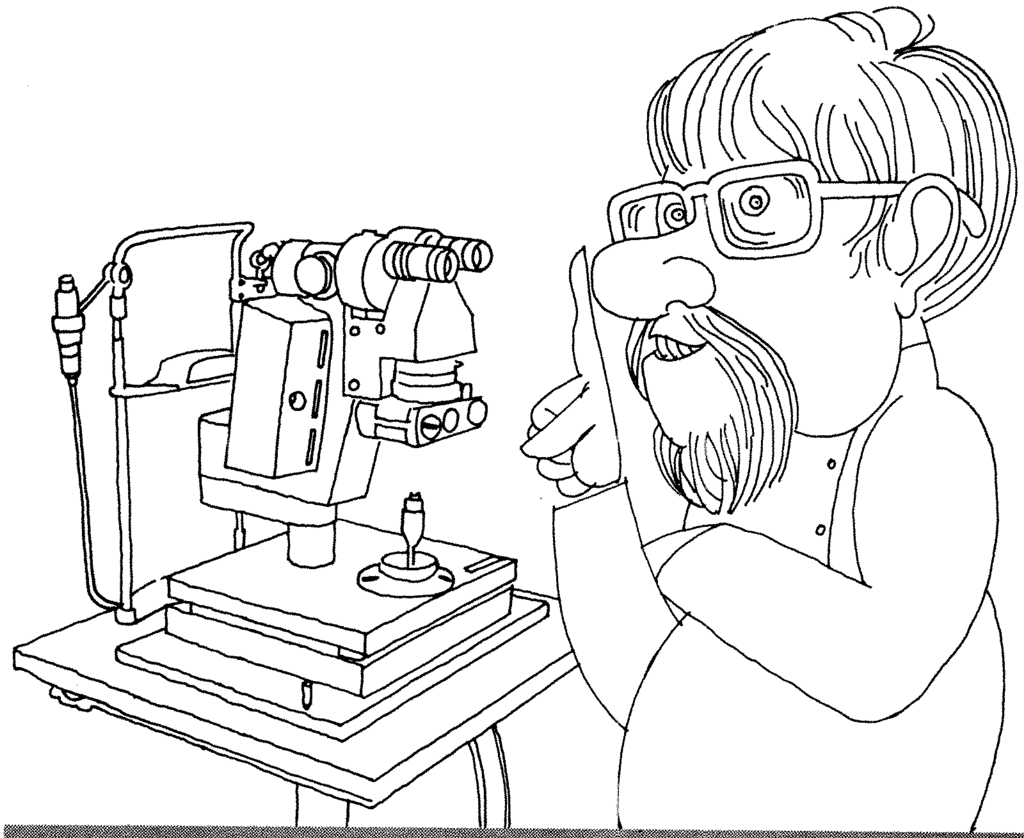

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British Journal of Ophthalmology

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Communications

Venous malformations in the orbit

G. A. S. LLOYD, J. E. WRIGHT, AND G. MORGAN

From the Department of Radiology, Moorfields Eye Hospital, and the Institute of Ophthalmology, University of London

The purpose of this paper is to present the clinical, radiological, and pathological findings in twelve patients presenting with orbital varices and to draw attention to the syndrome of congenital venous malformation in the orbit: a condition which may be associated with venous malformations elsewhere in the body. With the introduction of modern radiological methods of contrast investigation, particularly orbital venography, a more detailed demonstration of these lesions in the orbit and their vascular connections is now possible.

Case material

Nine patients seen in the *X* ray Department at the City Road Branch of Moorfields during the period of 1966–1970 have been shown to have venous malformation in the orbit, either by radiology or at surgical exploration. All these were investigated by angiography—either by carotid angiography, or by orbital venography, or both. Three other cases seen before this period and described by Lloyd (1965) have been added to the series; they did not have angiographic studies but are included because of their clinical and radiological similarity to the other nine cases.

The clinical, radiological, and pathological details are set out in the Table (overleaf), and may be summarized as follows:

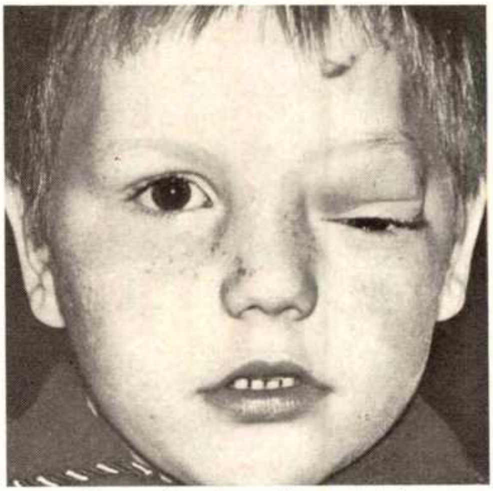

FIG. 1 *Case 3. Vascular swelling in the left forehead*

Clinical findings

The characteristic clinical picture was that of a child, adolescent, or young adult with a history of proptosis usually dating from birth or early childhood. The proptosis was normally provoked or made worse by an increase in the venous pressure in the head and neck. Vascular abnormalities were present in 75 per cent. affecting the conjunctiva or eyelids, and in three patients abnormal veins and localized venous dilatations were found on the forehead and scalp (Fig. 1). In one patient (Case 4) there was a venous abnormality of the hard palate.

Received for publication March 3, 1971
Address for reprints: G. A. S. Lloyd, *X* Ray Department, Moorfields Eye Hospital, City Road, London, E.C.1

Table

Case no.	Age (yrs)	Sex	Clinical summary	X ray findings		Operations	Pathology
				Plain films	Contrast studies		
1	29	M	Proptosis and occasional diplopia since childhood Soft reducible mass present in inner part of upper eyelid.	Enlarged orbit with solitary orbital phlebolith Abnormal venous 'lakes' in frontal bone		Orbital decompression only No full exploration of the orbit	
2	15	F	Protrusion and redness of the right eye from birth Gradual increase in severity of signs despite radiotherapy Fullness of right upper lid with enlarged venous malformation at inner canthus Partial iris coloboma with episcleral vascular swelling in lower fornix extending to limbus from 3 to 6 o'clock Right optic atrophy	Enlarged orbit with solitary extraorbital phlebolith in pterygoid plexus Abnormal venous 'lakes' in frontal bone		Excision of conjunctival and episcleral varices Catholysis to enlarged veins in upper lid	Lesion composed of dilated venous channels lined by single layer of endothelium Few arterioles Prominent connective tissue stroma with lymphocytes
3	5	M	Vascular swelling of left forehead, both eyelids, and left orbit from birth 5 mm. proptosis Left globe displaced downwards 6 mm., laterally 4 mm. (Fig. 1)	Orbit enlarged Abnormal venous 'lakes' in frontal bone	Carotid angiography showed multiple intracranial arterio-venous malformations No abnormality in affected orbit apart from abnormal origin of middle meningeal artery Orbital venography (at orbitotomy) showed large varix (Fig. 2)	Extended lateral orbitotomy revealed grossly enlarged superior orbital venous system with extension of enlarged vessels round levator and superior rectus muscles. Abnormal veins excised and main vein ligated at orbital apex	Lesion composed of dilated venous channels and many small arteries (Fig. 3)
4	13	M	Red right eye from birth Fullness of right upper eyelid with subconjunctival vascular swelling near nasal and temporal limbus Right eye was proptosed 3 mm., displaced downwards 4 mm., laterally 3 mm. Associated vascular abnormalities on right side of hard palate and scalp	Enlarged orbit with multiple phleboliths in orbit (Fig. 4) Abnormal venous 'lakes' in frontal bone	Arteriography showed displacement of ophthalmic artery only Injection of superficial varix showed abnormal collection of venous channels in orbit (Fig. 5)	No surgery	
5	11	M	Swelling of right lower lid noticed at age 3 Bluish swelling deep to skin of right lower lid enlarged on Valsalva	Soft tissue swelling visible with solitary phlebolith	Venography showed small varix demonstrated by direct injection (Fig. 6)	Varix was excised through incision in inferior fornix	Lesion consists of dilated and thrombosed vein

			diplopia and slight pain on looking up Right eye proptosed 3 mm. and displaced downwards 2 mm. Signs and symptoms gradually resolved over 3 wks Two previous similar episodes at age 14 and 17	orbit Abnormal vascular calcification	corresponding with site of vascular calcification Venography failed		
7	16	F	Increasing proptosis for 10 years with occasional sudden increases in degree of proptosis Subconjunctival vascular malformations Right eye displaced downwards 3 mm.	Enlarged orbit with two phleboliths	Arteriography failed to show any abnormality Venography showed dilated superior ophthalmic vein and partial filling of varix medially in orbit (Figs 7 and 8)	No surgery	
8	26	F	Left proptosis since birth with subconjunctival vascular swellings	Enlargement of left orbit	Arteriography not performed Venography showed abnormal veins in lateral and posterior part of orbit (Fig. 9)	No surgery	
9	74	F	Enlarged left upper eyelid since childhood Recent deterioration of vision and heaviness of eyelids Swelling of left upper eyelid enlarged on stooping and Valsalva Subconjunctival varices in left upper and lower fornices	Enlargement of left orbit with numerous phleboliths Abnormal calcification immediately above and to left of pituitary fossa		No surgery	
10	54	M	Periodic redness and watering of right eye for 20 years Right-sided proptosis of 4 mm.	Negative	Orbital venography showed a collection of varices in line of inferior ophthalmic vein communicating with pterygoid plexus (Fig. 10)	No surgery	
11	20	M	Double vision on looking left for 4 yrs Right eye proptosed 5 mm. and displaced downwards 3 mm. Elevation of globe restricted	Negative	Arteriography showed varix in anterior part of orbit and reflux filling of superior ophthalmic vein from cavernous sinus on later films Orbital venography showed no filling of orbital veins on affected side	Lateral orbitotomy showed an abnormally distended venous system in posterior part of orbit	Venous anomaly composed of thickened and dilated varicose channels one thrombosed One channel occluded by compression due to stromal fibrosis prominent throughout lesion Vein walls composed predominantly of connective tissue with sparse elastic fibres Thin internal elastic lamina well seen (Figs 11, 12, 13)
12	17	F	1 mth swelling in left upper lid Similar swelling noticed twice before, each lasting 2 to 3 mths Cystic firm blue subcutaneous swelling near trochlea No proptosis or displacement of globe	Negative	Non-filling of first part of superior ophthalmic vein	Thrombosed varix of first part of left superior orbital vein excised through brow incision	Simple dilated venous channel containing thrombus (Fig. 14)

Radiological findings

PLAIN X-RAY CHANGES

These varied with the extent of the venous abnormality, but the following signs were apparent in this series.

(1) Enlargement of the affected orbit (8 patients).

(2) Presence of one or more phleboliths in the orbit (6 patients) or extraorbital phleboliths (1 patient).

(3) Large venous lakes or vascular markings in the frontal bone on the affected side corresponding to the venous enlargements found clinically (4 patients).

(4) In one case there was vascular calcification in the orbit (Case 6) and in another (Case 9) a similar type of calcification was observed intracranially above the pituitary fossa.

CONTRAST INVESTIGATION

On carotid angiography no arterial abnormality was found other than displacement of vessels in the orbit, but in two patients it was possible to demonstrate abnormal veins in the orbit by subtraction studies of the later venous phase of the arteriogram (Cases 6 and 11). As might be expected the most diagnostically rewarding examination was orbital venography, and eight patients were examined by this method. In some only a solitary varix (Fig. 2) was demonstrated, while in others there was a collection of abnormal venous spaces in the orbit. (Fig. 5). The varices had no direct connection with the arterial side of the circulation and were often, to a large extent, divorced from the main venous circulation in the orbit. The presence of phleboliths implies venous stagnation (Hager,

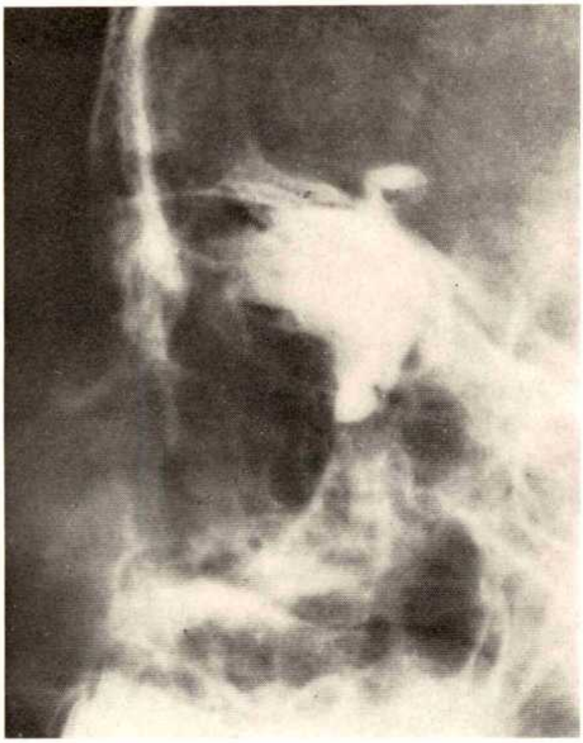

FIG. 2 *Case 3. Lateral radiograph of orbit, showing a large varix; contrast medium was injected directly into varix at orbitotomy*

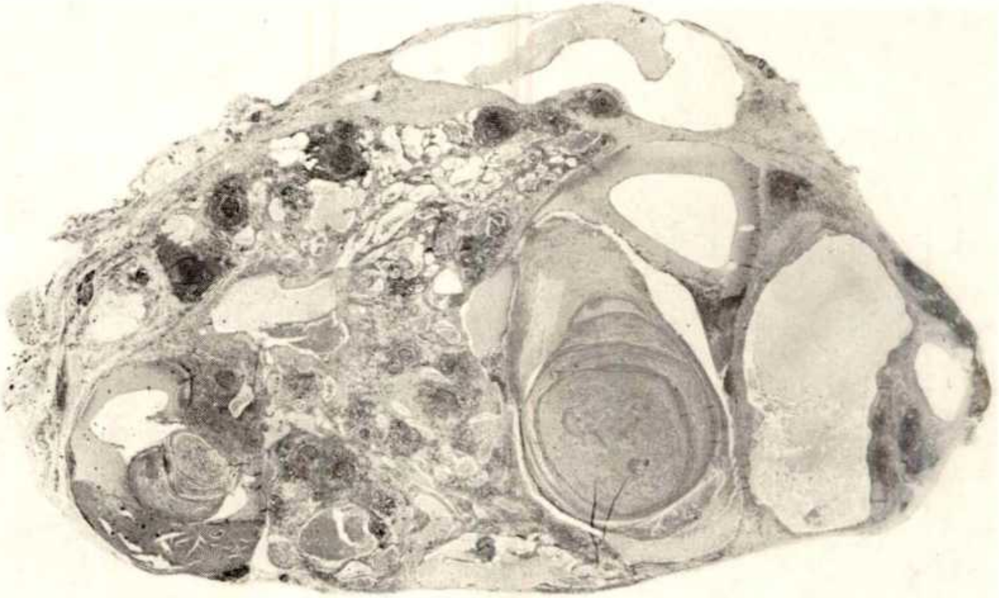

FIG. 3 *Case 3. Lesion composed of dilated venous channels, small arteries, and lymphocytic foci in stroma, some of the latter showing germinal centres. Haematoxylin and eosin.* ×5·5

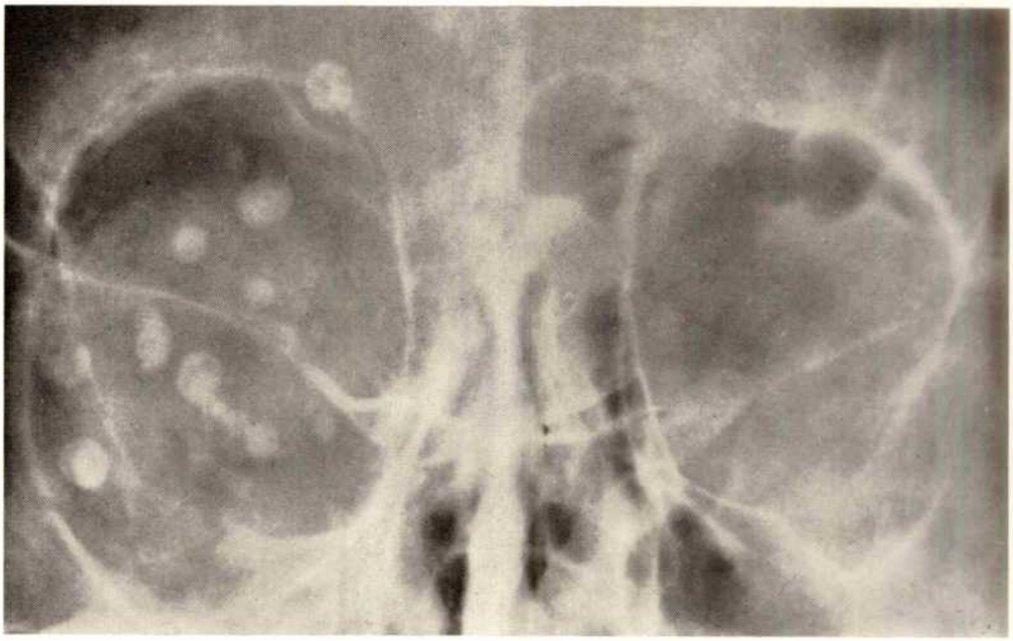

FIG. 4 *Case 4. Radiograph of enlarged right orbit with multiple phleboliths*

1958) and we were able to demonstrate this on orbital venography in a varix in the orbit of a 15-year-old girl (Case 7) (Figs 7 and 8). In this patient contrast remained in the varix outlining its upper and posterior surface some 5 minutes after the time of the original injection into the orbital venous system.

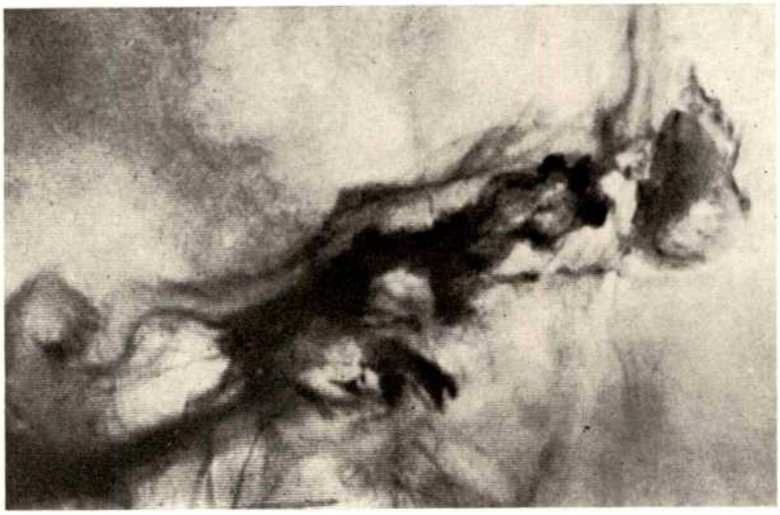

FIG. 5 *Case 4. Lateral subtraction film, showing abnormal venous channels in the upper orbit*

(6)

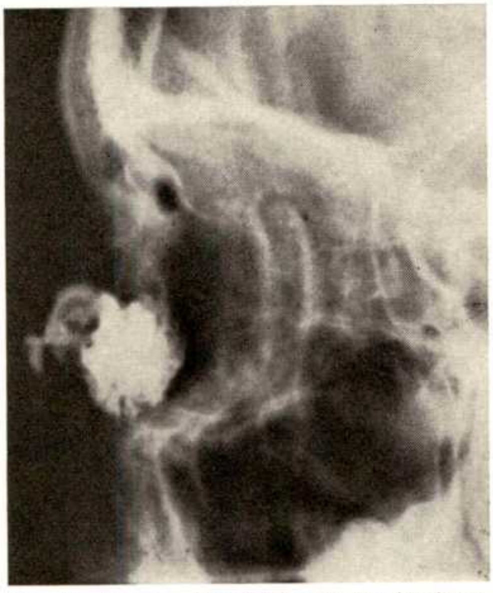

FIG. 6 *Case 5. Superficial varix in orbit demonstrated by direct injection (lateral projection)*

(7)

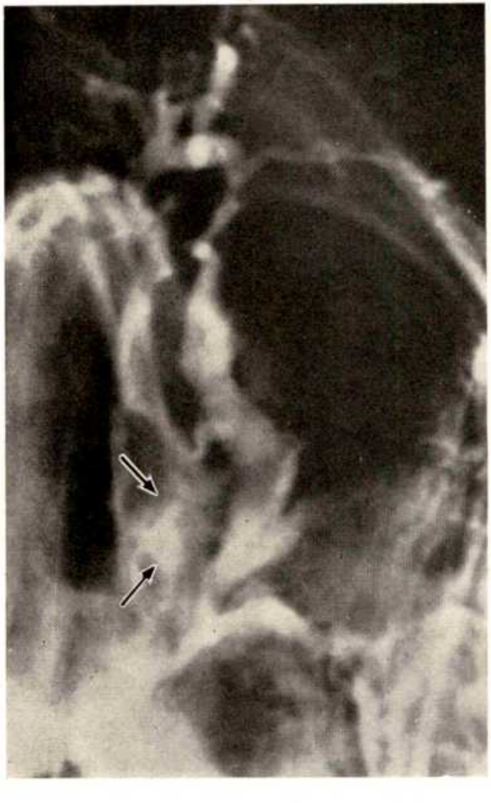

FIG. 7 *Case 7. Venogram (axial projection), showing dilated superior ophthalmic vein and a varix situated medially in orbit (arrowed)*

Histopathology

The essential pathological changes were a single dilated venous channel as in Cases 5 and 12 or several dilated venous channels as in Cases 3 and 11 (Figs 3, 11, 12, and 13). Thrombosis of these veins had occurred in Cases 5, 11, and 12 (Fig. 14). In addition, stromal fibrosis had compressed one of the veins in Case 11, and Cases 2 and 3 were charac-

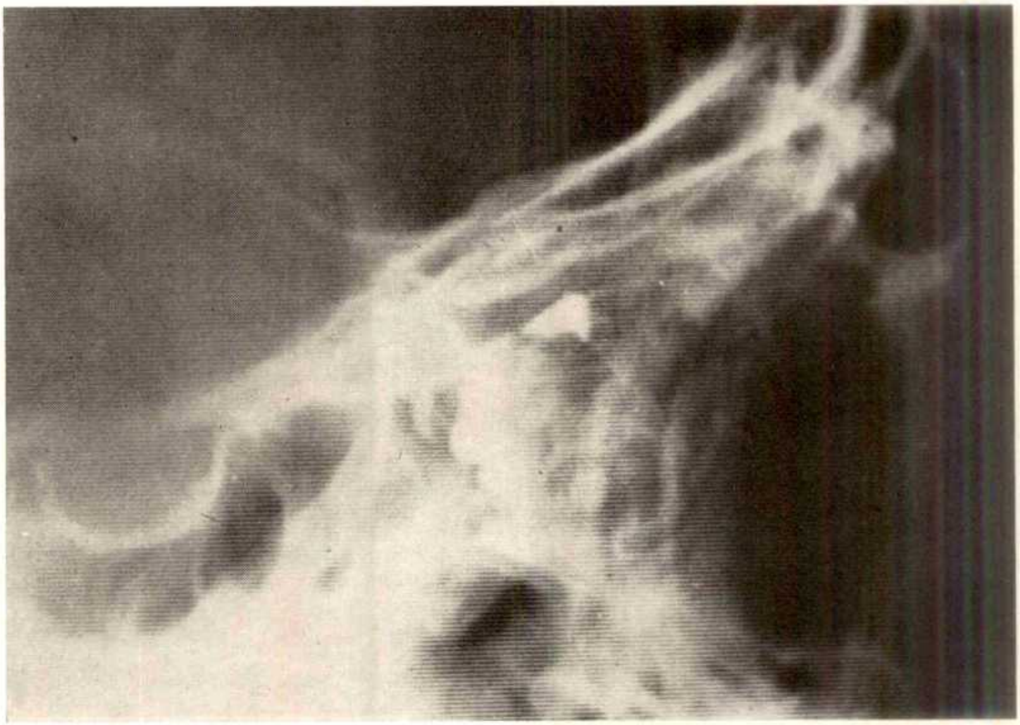

FIG. 8 *Case 7. Lateral view, showing pooling of contrast medium in orbital varix. This film was taken 5 min. after intravenous injection of contrast medium*

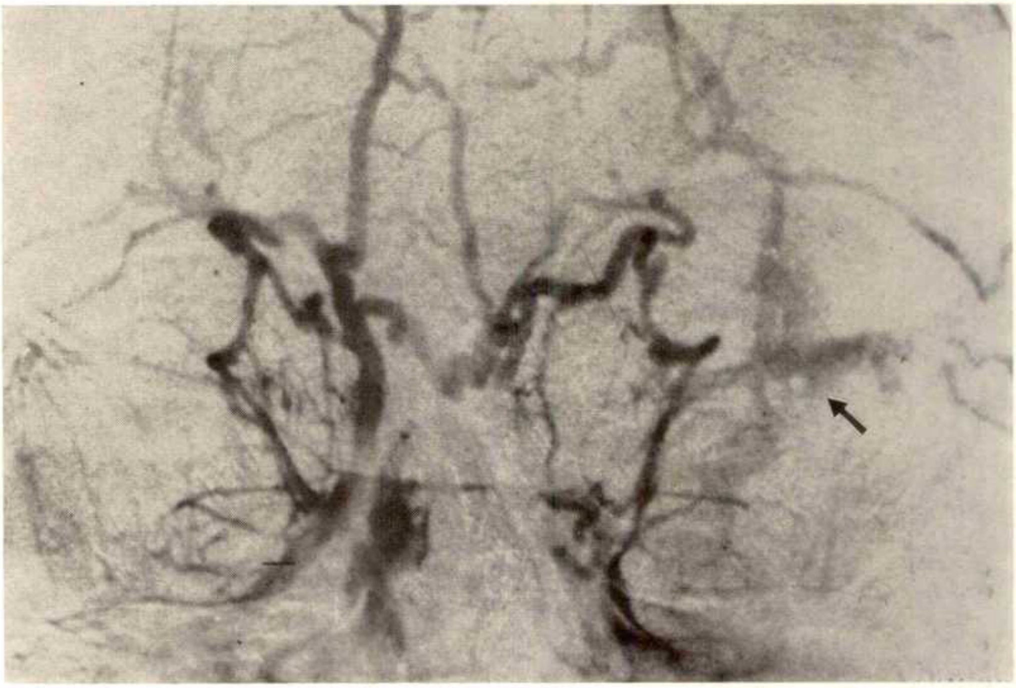

FIG. 9 *Case 8. Abnormal venous channels (arrowed) demonstrated in lateral part of left orbit at orbital venography (subtraction film)*

terized by lymphocytic infiltration of the stroma between the vessels. Although small arteries were seen in Cases 2 and 3, there was no evidence of an arteriovenous communication in any of the five cases.

(10)

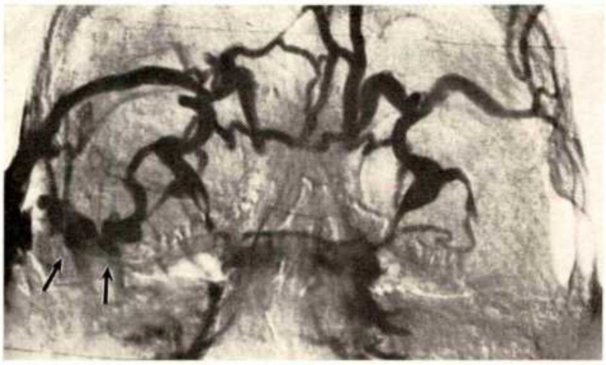

FIG. 10 *Case 10. Varices in lower temporal quadrant of right orbit (arrowed) draining into pterygoid plexus*

(11)

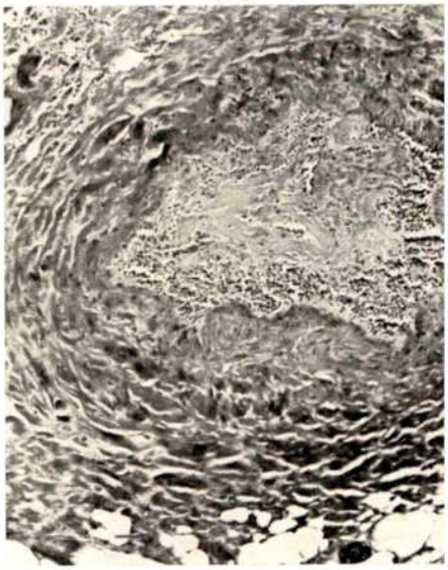

FIG. 11 *Case 11. Vein showing a connective tissue wall and sparse elastic fibres. Verhoeff-van Gieson.* ×80

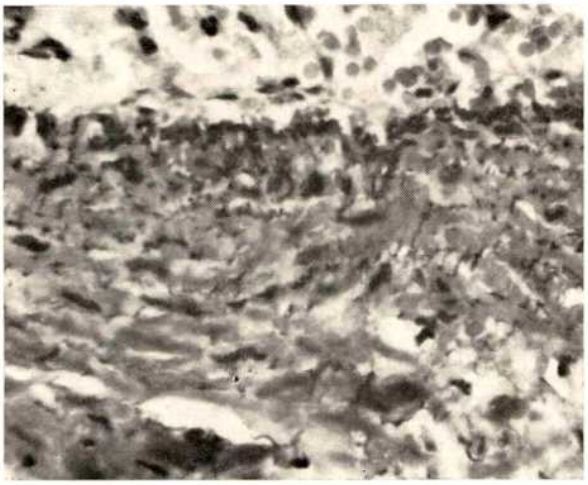

FIG. 12 *Case 11. Part of wall of vein, showing internal elastic lamina. Verhoeff-van Gieson.* ×440

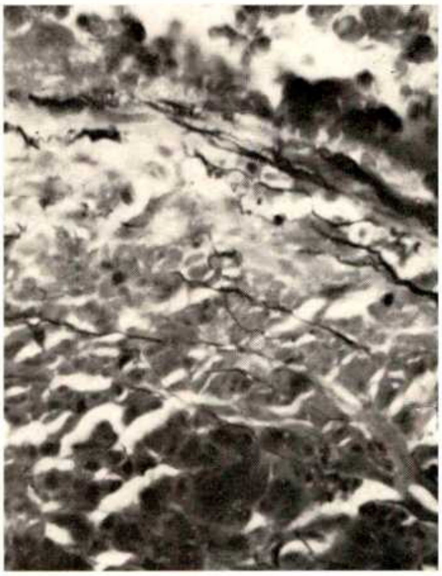

FIG. 13 *Case 11. Part of wall of vein, sh sparse elastic fibres. Verhoeff-van Gieson.* ×

Discussion

Early writings concerning orbital varices consist, for the most part, of clinical descriptions of single cases without surgical or pathological proof of the presence of abnormal orbital

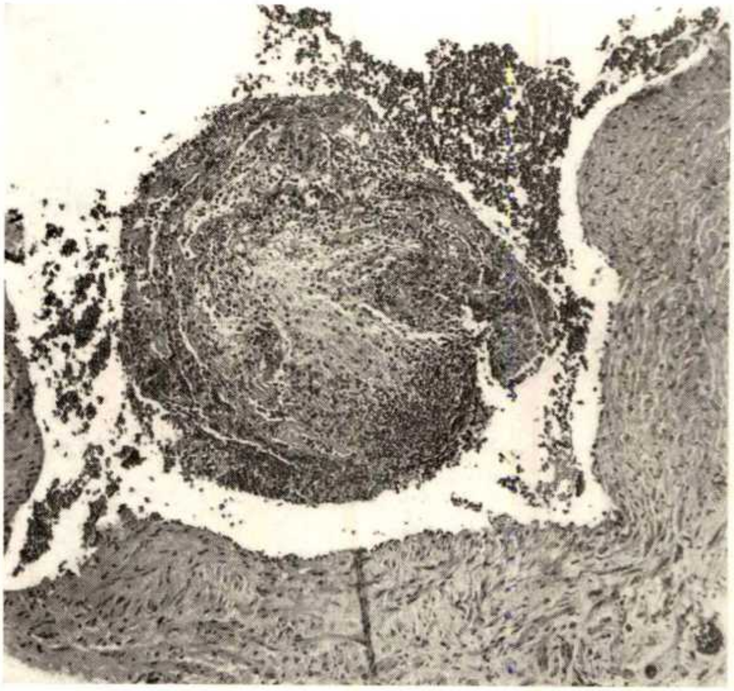

FIG. 14 *Case 12. Portion of wall of vein, containing thrombus. Haematoxylin and eosin.* ×70

veins or of their origin. In these patients the diagnosis of orbital varices was inferred clinically because of the presence of intermittent proptosis, associated in some patients with visibly dilated veins in the anterior orbit. Reports of varices proven at surgery were given by Lowenstein (1911), Germain and Weill (1928), and Rumjanzewa (1930), but in none of these records of operations was there any mention of the possible aetiology of the venous enlargement.

It was not until the report of a case of intermittent proptosis and orbital varices by Walsh and Dandy (1944) that a definite cause was discovered. In this patient the varices were shown, at craniotomy, to be secondary to an arteriovenous malformation in the middle fossa. Duke-Elder (1952), quoting this patient, suggested that this may be the cause in many, if not all such cases. On the other hand, Hobbs, du Boulay, and Davis (1960), reporting a case of cavernous haemangioma, regarded orbital varices as a more fully developed form of haemangioma. It has already been pointed out (Lloyd, 1965) that neither of these theories could account for all types of varix found in the orbit, since these could be either:

(*a*) Primary: due to a congenital venous malformation in the orbit.

(*b*) Secondary to an arteriovenous shunt, either intracranially or within the orbit itself.

CONGENITAL VENOUS MALFORMATION

We believe the twelve patients described belong to this category and form a recognizable clinico-radiological entity distinct from secondary orbital varices. A typical description of the clinical features of this syndrome was given by Magnus (1884) and more recently by Hu Yung-Lin and Shih Chen-Jung (1954). The latter authors recorded a 26-year-old patient with intermittent proptosis and phleboliths in the right orbit. This was associated with venous abnormalities on the forehead and eyebrow, and similar masses and large varicose veins over the right side of the abdomen and on the right upper arm and leg. Other authors have described patients with associated venous abnormalities outside the orbit: on the buccal mucosa (Gastreich, 1932; Marchesini, 1935); involving the upper and lower limbs (Kira, 1932). The venous malformation may, in some patients, extend into the middle fossa (Hanafee, Shiu, and Dayton, 1968). Brauston and Norton (1963) also described a patient with a venous malformation in the orbit which extended backwards to an enlarged sphenoidal fissure. In four patients in our series there was clinical or radiological evidence of extension outside the orbit, usually involving the scalp and frontal bone on the affected side, but one patient (Case 4) had a venous abnormality of the hard palate. These four patients can be regarded as examples of the full syndrome, *i.e.* orbital varices and associated venous malformations outside the orbit, but in the remaining patients we believe that essentially the same abnormality was present but confined to the orbit. Aron-Rosa and Offret (1967), in recording six cases of orbital varices demonstrated by orbital phlebography, described one case of the Klippel-Trenaunay syndrome, which was associated with a venous angioma of the orbit and eye, and it would seem that the condition we have described in the orbit may be related to, or be part of, the Klippel-Trenaunay syndrome.

SECONDARY ORBITAL VARICES

During the period in which this series was collected, three patients were investigated in the *X* ray Department for orbital varices and were shown to have a carotico-cavernous fistula of non-traumatic origin causing secondary dilatation of the otherwise normal venous system in the orbit. These patients for the most part are easily distinguishable on clinical grounds from cases of primary or congenital varices. Another and clinically less distinguishable cause of secondary dilatation of orbital veins is an arteriovenous malformation, which may be situated either within the orbit itself or intracranially. The first recorded case was that of Walsh and Dandy (1944), who described an 18-year-old girl with intermittent proptosis and dilatation of the intraorbital veins due to an arteriovenous malformation in the middle fossa. More recently de Lima and Penzholz (1968) have published a case in which orbital varices were shown at surgery to be associated with an arteriovenous malformation in the anterior fossa of the skull, lying immediately above the orbital roof, through which the dilated orbital veins communicated directly with the malformation. Examples of arteriovenous malformations within the orbit giving rise to orbital varices are more numerous. Jacas, Ley, and Campillo (1959) published the arteriograms of a 31-year-old patient with intermittent proptosis and orbital varices due to an arteriovenous malformation in the orbit. Intraorbital arteriovenous malformations have also been recorded in the literature by Huber (1951), Krayenbühl (1962), Lombardi (1967), and Aron-Rosa and Offret (1967). In these patients varices may either be dilated normal veins or may consist in part of the venous component of the arteriovenous malformation.

In one patient in this series (Case 3), a large solitary orbital varix was associated with small, multiple intracranial arteriovenous malformations; however, since these were remote from the orbit containing the varix and there was no demonstrable connection between them, it was felt that the vascular anomalies were not causally connected, and that the orbital varix should be classified as a primary venous malformation.

Conclusion

The classification of orbital varices into primary (congenital venous malformation) and secondary (due to an arteriovenous shunt) is in accord with the view expressed by Walsh and Dandy (1944) that:

> "It is possible that there are two general types of lesion causing intermittent exophthalmos: (*i*) Arterio-venous with pulsation, and (*ii*) Venous without pulsation."

This statement, though generally true, needs some qualification on the clinical side, since an arteriovenous malformation, even when present within the orbit, may not produce a pulsating exophthalmos, nor indeed is this a constant feature of a carotico-cavernous fistula. On the other hand, pulsating exophthalmos has been reported in a patient with an entirely venous malformation in the orbit by Brauston and Norton (1963), who considered it to be due to an enlargement of the sphenoidal fissure allowing transmission of cerebral pulsation to the orbital contents. It is thus not possible to be certain of the aetiology of orbital varices in a given case on clinical grounds alone, nor are the plain-*x* ray changes pathognomonic, although it would seem that the presence of phleboliths is almost diagnostic of a venous malformation. It is therefore essential to investigate patients by angiography before any treatment is considered.

In the presence of a bruit or pulsating exophthalmos indicating the likelihood of an arteriovenous shunt, carotid arteriography is the method of choice, whereas an intermittent exophthalmos without pulsation or bruit should be investigated in the first instance by orbital venography, either by the frontal vein technique (Vritsios, 1963) or by direct injection of a superficial varix (Fig. 6). The presence of enlarged orbital veins as a cause of proptosis should be recognized if the appropriate contrast studies are undertaken. Frontal venography now enables us to differentiate several types of venous abnormality within the orbit and thus places their treatment on a more rational basis.

Our thanks are due to the surgeons of Moorfields Eye Hospital for allowing us to present their cases, to Prof. Barrie Jones for his help and encouragement, and to Miss R. Rhodes for her secretarial assistance.

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Visibility of transparent objects in the eye by retroillumination

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Retroillumination is performed at the slit-lamp with the binocular microscope focused upon the object which is illuminated from behind by the slit-lamp beam reflected off some structure posterior to the object (Vogt, 1930). Objects in the cornea and lens are observed in this way and the reflectors used are the iris, the lens, or the fundus. The use of the ophthalmoscope for retroillumination of the cornea is also described (Chandler, 1945).

Objects are visible because they interfere with the emergent light from the eye by obstruction, refraction, respersion (Berliner, 1943), and reflection. Transparent objects are visible by retroillumination when the refractive index of the object is above or below that of the surrounding medium. The property mainly responsible is refraction, but reflection also plays some part. The observed appearance changes with the direction of the retroillumination and with the refractive nature of the object. From the appearance of an object under varying retroillumination conditions, conclusions can be drawn about the refractive nature of the object. Although a variety of combinations of shapes and refractive indices are possible in the object, these can be resolved into only two observable effects:

(1) The object acting as a diverging refractor (lens or cylinder).

(2) The object acting as a converging refractor (lens or cylinder).

Clinical examples are shown in macrophotographs made by the technique previously described (Brown, 1970). Photographs are shown for comparison of a diverging lens (plano-concave) and of a converging lens (plano-convex) (Fig. 2). A model has been constructed to resemble objects found in the eye. The model has two spherical objects imbedded in a clear medium (gelatin); one object of low refractive index (air) which acts as a diverging lens, and one of high refractive index (liquid paraffin) which acts as a converging lens. Photographs are shown of the model under varying conditions of illumination (Figs 3, 4, and 5).

Methods of retroillumination

MARGINAL RETROILLUMINATION (Graves, 1924)

This is produced by illuminating half the field behind the object, with the object placed in front of the conjunction between light and dark areas. This can be achieved by using the edge of the decentred slit beam, or by using a natural boundary such as the pupil margin.

The distribution of light within the object is seen to take one of two forms:

(1) Unreversed: the distribution is the same as that of the background.

(2) Reversed: the distribution is opposite to that of the background.

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The unreversed effect is produced by an object acting as a diverging refractor and the reversed effect by a converging refractor, provided that its focal length is shorter than the distance between the object and the area of retroillumination. The optical explanation of the effect is shown in Fig. 1A.

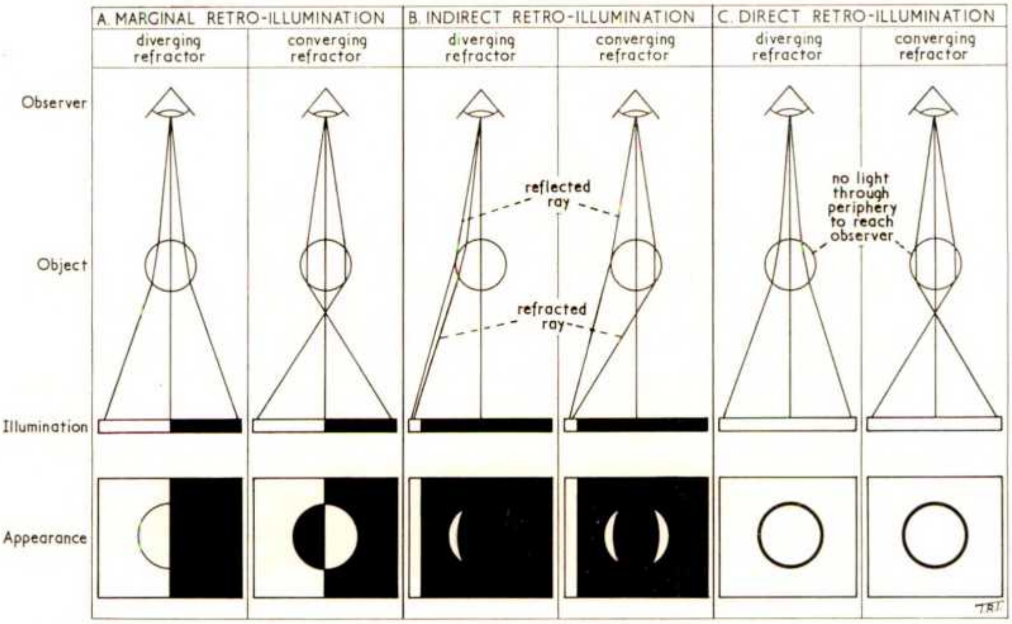
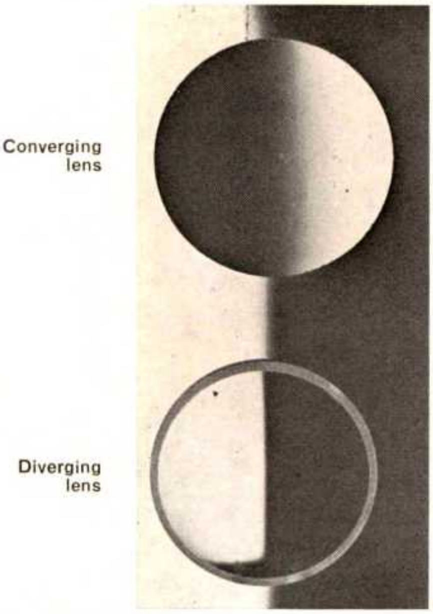


FIG. 1 *Optics of retroillumination*

2



3

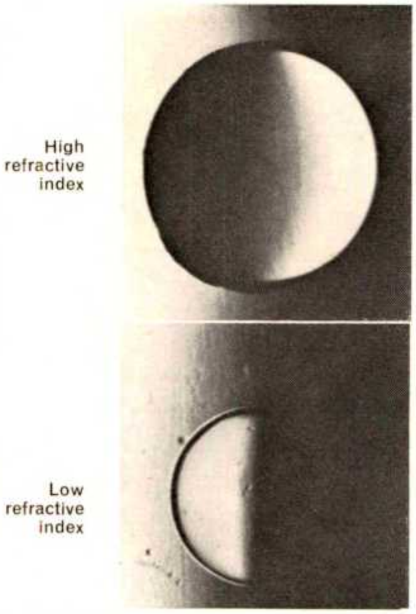
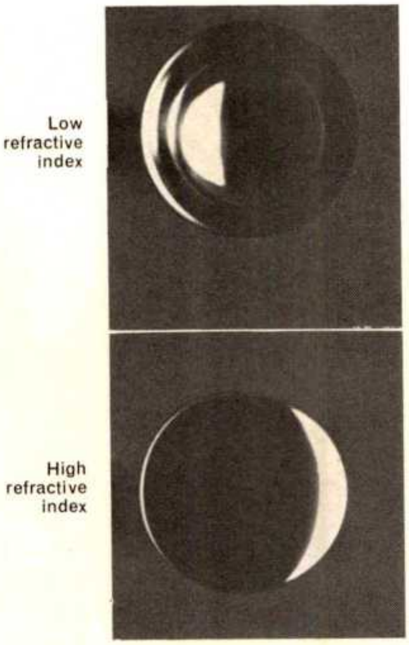


FIG. 2 *Lenses. The diverging lens shows the unreversed effect. The converging lens shows the reversed effect*

FIG. 3 *Model. Marginal retroillumination. The low refractive index object shows the unreversed effect. The high refractive index object shows the reversed effect*

4



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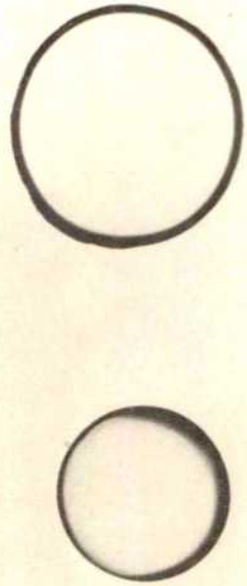


FIG. 4 *Model. Indirect retroillumination. The low refractive index object shows refracted and reflected light on one side. The high refractive index object shows reflected and refracted light on opposite sides*

FIG. 5 *Model. Direct retroillumination. Both objects show dark edges*

In the photograph of the lenses (Fig. 2) the unreversed effect is seen in the diverging lens and the reversed effect in the converging lens. In the model (Fig. 3), the unreversed effect is seen in the object of low refractive index and the reversed effect in the object of high refractive index.

Clinical examples of spherical objects showing the unreversed effect are shown in Figs 6 and 7 and the reversed effect in Figs 8 and 9. Cylindrical objects showing the unreversed effect are shown in Figs 10 and 11 and the reversed effect in Figs 12 and 13.

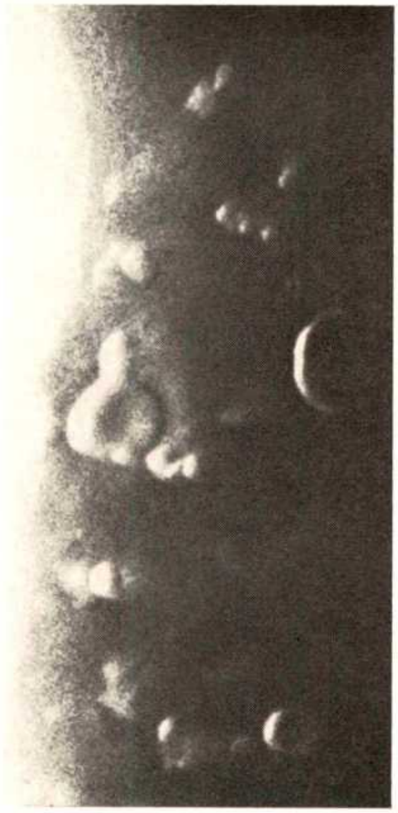
Vogt (1930) recognized that cystic objects reversed light, and he used as an example a photograph of rain drops upon a window. Graves (1924) was able to separate the appearances into unreversed and reversed effects and suggested that this was due to the refractive nature of the object.

INDIRECT RETROILLUMINATION (Berliner, 1943)

This is produced by displacing the retroillumination to one side of the object, so that the object is observed against a dark background. When this is done the unreversed or reversed effects become limited to crescents in spherical objects and to the marginal region in cylindrical objects. These effects may be seen alone, and also in conjunction with surface reflections (described below) as is seen in the photographs of the model (Fig. 4). The optics of indirect retroillumination are shown in Fig. 1B.

Clinical examples showing crescents are seen with the unreversed effect in Figs 6 and 14, and with the reversed effect in Fig. 8. A cylindrical object showing the reversed effect limited to the marginal region is shown in Fig. 13.

(6)



(7)

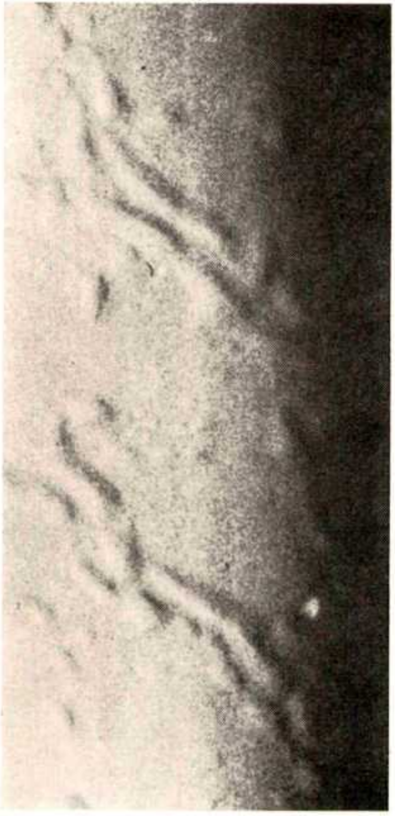


FIG. 6 *Intraepithelial cysts. Marginal and indirect retroillumination unreversed effect and reflections*

FIG. 7 *Net-like dystrophy. Marginal retroillumination. Unreversed effect*

Surface reflections occur with both spherical and cylindrical objects observed by indirect retroillumination. The reflection occurs on the same side as the illumination, so that the reflection contributes to the crescent of the unreversed effect, but is on the opposite side to the reversed effect. The converging type of spherical object therefore shows two bright crescents, one on each side. The optics of reflections are shown in Fig. 1B. With the low refractive index object, this is by total internal reflection within the denser medium, and with the high refractive index object it is a surface reflection off the object.

Reflections are seen in the photograph of the model (Fig. 4), and in clinical examples of spherical objects (Figs 6 and 8), and of a cylindrical object (Fig. 13).

DIRECT RETROILLUMINATION

The object is illuminated by an evenly lit background directly behind it. The object is then distinguished from the background by a dark edge which is present for both converging and diverging objects. The luminosity of the central parts of the object appear similar to the background illumination. In practice it is not easy to produce a perfectly evenly lit background, so that the dark edge effect is usually combined with the unreversed or reversed effects.

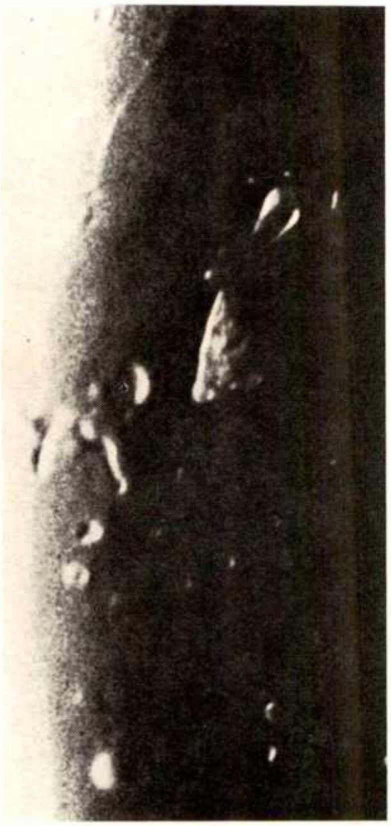


FIG. 8 *Intraepithelial cysts. Marginal and indirect retroillumination. Reversed effect and reflections*

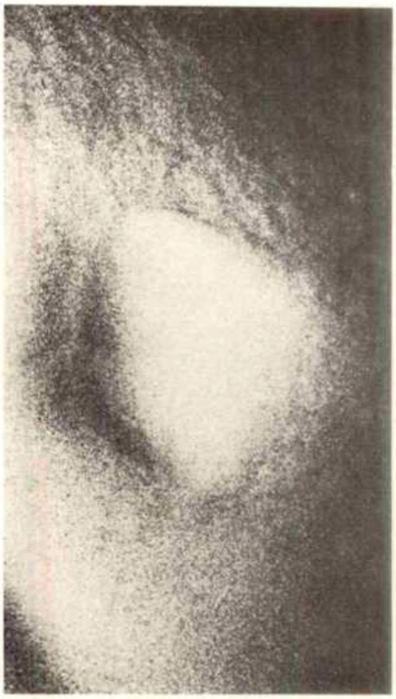


FIG. 9 *Epithelial bulla. Marginal retroillumination. Reversed effect*

The dark edge is accounted for by rays being unable to pass through the periphery of an object, acting as a thick lens to reach the observer (Fig. 1C).

The dark edge is shown by the spherical objects in the model (Fig. 5); the clinical example in which it is best seen is Fig. 15.

Discussion

The effects seen in transparent objects are resolvable into:

(**1**) Objects acting as a diverging refractor.

(**2**) Objects acting as a converging refractor.

The ways in which these can be recognized have been described above.

The shape of the object can be confidently determined in some cases with additional clues from the appearance by focal illumination and from the disturbance of the tear film and of the specular reflex when present. When these clues are not available the shape of the object remains speculative.

The cornea is a substance of relatively high refractive index 1.376 (Matthiessen, 1891) compared to the aqueous of index 1.336 (Duke-Elder, 1938). The corneal epithelium has a higher refractive index than the stroma of 1.416 (Fischer, 1927).

The following types of object have refractive properties.

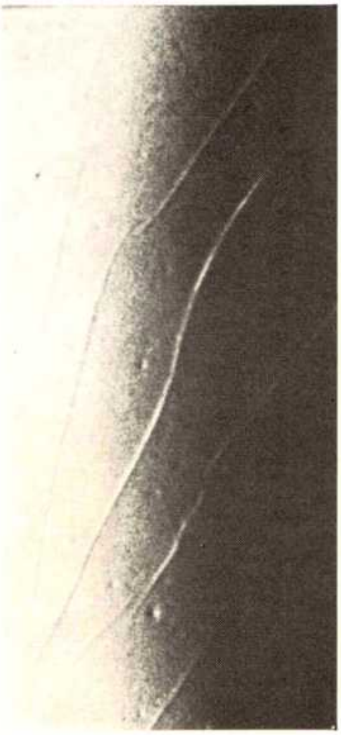


FIG. 10 *Finger print lines. Marginal retroillumination. Unreversed effect*

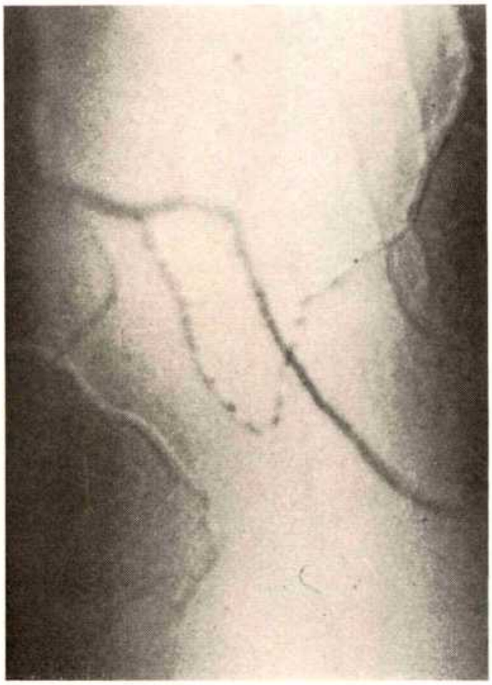


FIG. 11 *Stromal blood vessels. Marginal retroillumination. Unreversed effect*

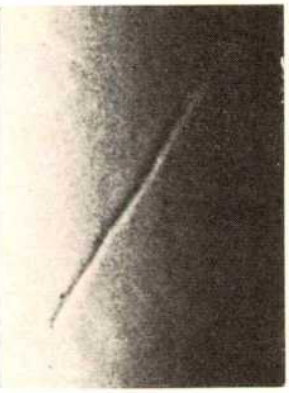


FIG. 12 *Stromal microfilaria. Marginal retroillumination. Reversed effect*

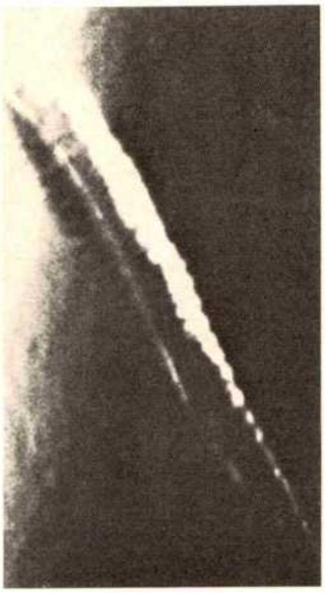


FIG. 13 *Descemet's splits. Marginal and indirect retroillumination*

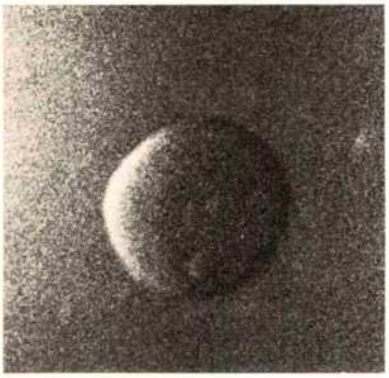


FIG. 14 *Lens cyst. Indirect retroillumination. Unreversed effect*

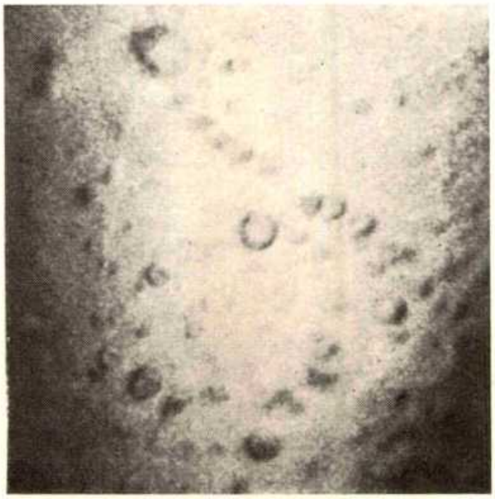


FIG. 15 *Intraepithelial cysts. Direct retroillumination. Dark edges*

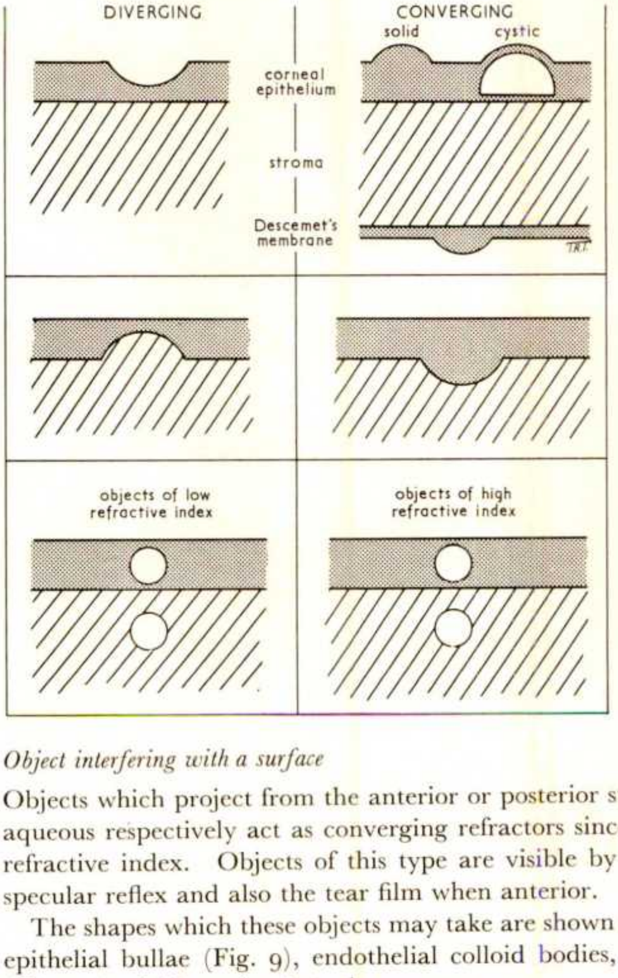


FIG. 16 *Shape of objects visible by retroillumination*

Object interfering with a surface

Objects which project from the anterior or posterior surfaces of the cornea into the air or aqueous respectively act as converging refractors since they project into regions of lower refractive index. Objects of this type are visible by focal illumination and disturb the specular reflex and also the tear film when anterior.

The shapes which these objects may take are shown in Fig. 16A. Clinical examples are epithelial bullae (Fig. 9), endothelial colloid bodies, and the so-called Descemet's splits (Fig. 13), which project into the aqueous.

Object projecting into a tissue of different refractive index

This type of object can occur wherever two adjacent tissues have different refractive indices, in particular at the junction of the corneal epithelium with Bowman's membrane. The objects act as diverging or converging refractors, depending upon whether they project into a zone of higher or lower refractive index. Clues to their shape are usually not available from other methods of examination.

The shapes which these objects may take are shown diagrammatically in Fig. 16B. Clinical examples are the fingerprint line (Fig. 10) and net-like dystrophy (Fig. 7), which both behave as diverging refractors.

Objects wholly within a tissue of different refractive index

This type of object is seen within the corneal epithelium, in the corneal stroma, and in the lens. When the refractive index of the object is lower than that of the surrounding tissue it acts as a diverging refractor, and when the refractive index of the object is higher it acts as a converging refractor.

The shape of this type of object is shown diagramatically in Fig. 16C and is imitated by the model. Clinical examples are intraepithelial cysts (Figs 6, 8, and 15), and blood vessels and microfilariae in the corneal stroma (Figs 11 and 12), and also the lens cyst (Fig. 14).

If the object of this type is large enough to disturb the surface it then acts as an object interfering with a surface such as the corneal bulla (Fig. 9).

I wish to thank Prof. Barrie R. Jones for giving me access to his patients and Mr. T. R. Tarrant of the Institute of Ophthalmology who prepared the diagrams.

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Clinical, biochemical, and immunoelectrophoretic study of subretinal fluid

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Subretinal fluid found in retinal detachments associated with retinal tears is derived from the vitreous, or from the choroidal vessels, or both. The relatively high concentration of protein found in subretinal fluid argues mainly in favour of the protein being derived from the choroidal vessels. Examinations of total protein concentration in subretinal fluid have been made by several workers. Smith and Douty (1960) and Heath, Beck, and Foulds (1962) found that the total protein concentration of the subretinal fluid tended to rise with an increase in the duration of the detachment. Heath & others (1962) felt that the rise in total protein concentration indicated an increasing permeability of the choroidal capillaries; they also found a marked increase in total protein in eyes which had undergone more than one operation. Weber and Wilson (1963) confirmed the protein findings and later stated (Weber and Wilson, 1966) that they thought the formation of subretinal fluid was a dynamic process. Cooper, Halbert, and Manski (1963), using immunoelectrophoresis, showed large numbers of serum proteins in the fifteen cases of subretinal fluid examined. Manuel, Royer, Richard, and Creyssel (1960), examining subretinal fluid by immunoelectrophoresis, found a "γ" precipitin band. Speiser (1964) used a similar technique in examining eleven cases and found serum-like proteins when the total protein concentration was high, but with lower protein concentrations the globulins were relatively reduced, and with very low total protein concentrations only albumin could be detected.

The purpose of this communication is to report the total protein concentrations and immunoelectrophoretic examinations of 28 specimens of subretinal fluid obtained from 26 patients suffering from retinal detachment. The technique of immunoelectrophoresis used in this study has enabled a more detailed examination of the subretinal fluid to be made than has hitherto been reported. It has allowed in particular a detailed examination of the γ-globulin fraction of the subretinal fluid. The presence or absence of IgG, IgA, and IgM may be detected, and thus it is possible to assess the degree of permeability of the choroidal capillaries and Bruch's membrane in retinal detachments.

Method

COLLECTION AT OPERATION

The area around the proposed site of scleral puncture was carefully dried. Scleral puncture was

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made immediately after the application of cryotherapy. Subretinal fluid was collected by placing dried, sterilized, 20-μl. glass capillary tubing in the stream of subretinal fluid emerging from the puncture site. These tubes were then sealed and stored at 4°C. and analysed as soon as possible.

ANALYSIS

Total protein

This was measured by micro-Kjeldahl digestion followed by nitrogen estimation with Nessler's reagent. To enable the protein electrophoretic pattern of the subretinal fluid to be compared with that of plasma from the same patient, a drop of fluid was concentrated by rapid evaporation in a stream of warm air. The concentrated fluid was then placed in one "foot" of the multiapplicator, the patient's plasma was placed in an adjacent foot, and cellulose acetate electrophoresis was performed with Ponceau S staining (Carruthers, 1970). The identical conditions for migration and staining enabled the subretinal fluid and plasma patterns to be correlated, both by inspection and by scanning on a Wooster Mark III Microdensitometer. The results obtained were expressed in g./100 ml.

IMMUNOELECTROPHORESIS

This was performed on agar plates based on the microtechnique proposed by Scheidegger (1955) as an improvement on the original technique of Grabar and Williams (1953). 8 ml. of 1·5 per cent. I.D. agar (oxoid) in veronal buffer (pH 8·2; I = 0·05) to which sodium azide was added to give a concentration of 1 : 1000 was poured over a previously coated 8 × 8 cu.cm. glass slide (Kodak) and allowed to set in a moist chamber overnight. Circular wells 1 mm. in diameter were cut along the middle of the plate 10 mm. apart and filled with subretinal fluid using a micropipette. Normal human serum was put into one of the wells for comparison. The plate was then put upside down on the shoulder piece of the electrophoresis tank (Shandon U77 after Kohn) and connected to electrode compartments containing barbitone buffer (pH 8·6; I = 0·075) by thick filter paper strips. The current was adjusted to 10 mA/per plate and allowed to run for 2 hrs. After electrophoresis the plate was removed and troughs (60 × 1 mm.) were cut equidistant between the wells, along the direction of electrophoretic migration. Strips of agar were removed by applying suction. The troughs were then filled with antihuman multivalent and monospecific sera and the plate was then left in a moist chamber for 2 days. The plate was then washed with 3 per cent. saline for 2 days to remove unprecipitated proteins. After further washing in distilled water for 4 hrs the plate was covered by lint-free filter paper and completely dried in an incubator at 37°C. After removal of the filter paper the plate was stained in 0·2 per cent. Ponceau S or 0·1 per cent. nigrosine to pick up fine precipitin lines, otherwise barely visible. According to the nature and number of precipitin lines, as compared with normal human serum the subretinal fluids were divided into three main groups:

Group A Possessed almost all the constituents of normal serum and showed prominent precipitin bands for albumin, α_1 antitrypsin, group-specific component (Gc)-globulin, haptoglobin, transferrin, haemopexin, IgG and IgA.

Group B Possessed all the constituents shown in Group A, with the exception of IgA which was absent.

Group C Possessed few of the constituents of normal human serum. Only albumin, traces of IgG, and transferrin were found.

Three cases showed the characteristics of Group B, but minute traces of IgA were found and they were indicated as belonging to Group A-B. Examples of the results obtained from immunoelectrophoresis are shown in Figs 1–4 (opposite and overleaf).

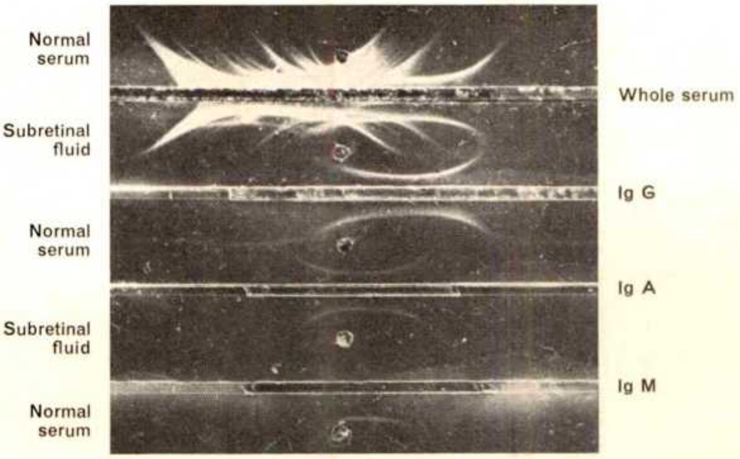

FIG. 1 *Sample of subretinal fluid tested against antihuman "whole" or multivalent serum (WS) and mono-specific sera against immunoglobulins G, A, and M. This sample would be classified under Group A as only IgM is absent*

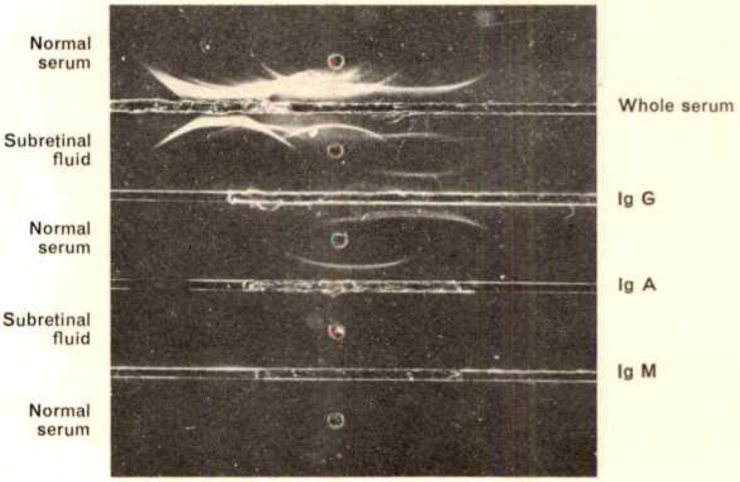

FIG. 2 *Subretinal fluid of Group B pattern, where IgA as well as IgM is absent*

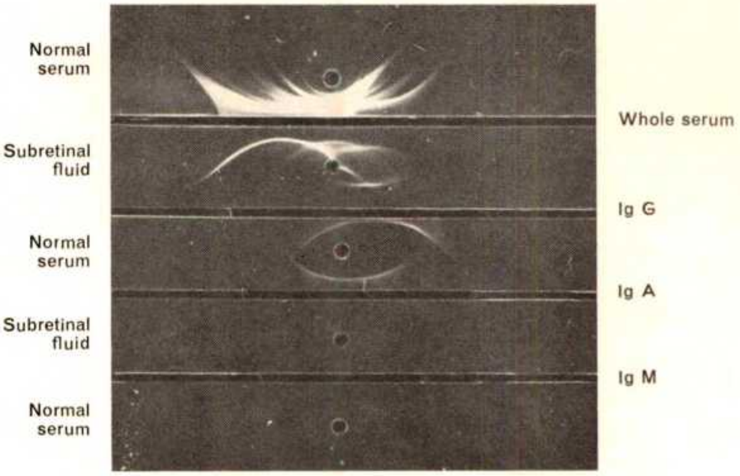

FIG. 3 *Subretinal fluid of Group C pattern, where albumin and only traces of IgG and transferrin are present*

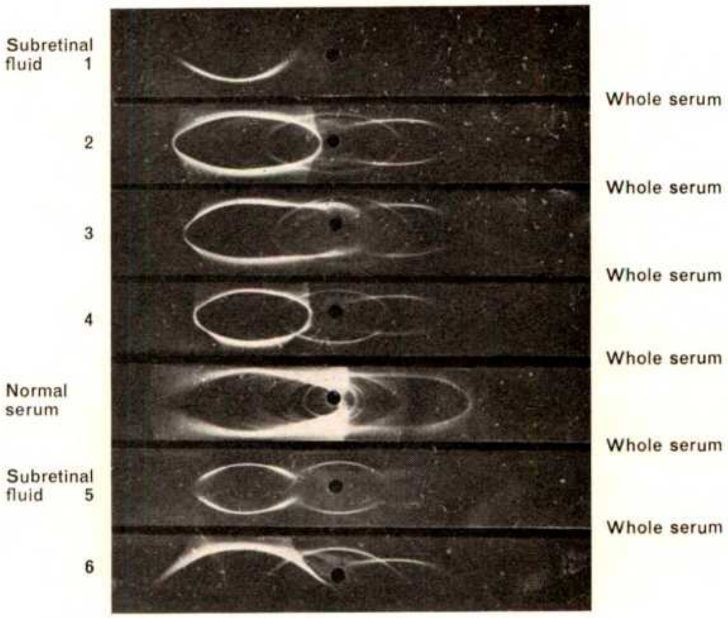

FIG. 4 *Group of six subretinal fluids, of which according to the classification described above, Nos* 2, 3, 4, *and* 6 *are Group B. No* 1, *showing only albumin and No.* 5, *showing all the fractions indicated in Fig.* 3, *are both Group C.*

Results (Table I, opposite)

The duration of the retinal detachment is indicated in weeks. Total protein is expressed in g./100 ml. Specific points of clinical interest are shown. Unless indicated, subretinal fluid specimens were obtained from patients undergoing an initial retinal detachment operation and retinal holes were found. One case of retinoschisis was studied.

EXAMINATION OF THE RESULTS SHOWS THE FOLLOWING:

(1) High levels of total protein concentration (71·5 g./100 ml.) are found in cases of long-standing retinal detachment (longer than 8 weeks), as shown in Table II.

Table II *Protein concentration of subretinal fluid related to duration of detachment*

Duration of detachment (wks)	*Total protein concentration (g./100 ml.)*					
	< 1·0		1–1·50		> 1·50	
	No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*
1–4 (13 cases)	7	53·8	6	46·2	0	0
8+ (12 cases)	6	50	2	16·7	4	33·3

(2) In the immunoelectrophoretic study there was a general tendency for subretinal fluid to come to resemble serum more closely, with increasing duration of detachment (*i.e.* towards Group A with increasing age), as shown in Table III (overleaf).

(3) There does not appear to be a constant relationship between immunoelectrophoresis grouping and total protein concentration. High total protein concentration may be associated with immunoelectrophoretic Group A (Cases 21, 24, and 26) or Group C

Table I *Results in 28 specimens obtained from 26 patients*

Case no.	*Duration of detachment (wks)*	*Total protein (g/100 ml.)*	*Immuno-electro-phoretic group*	*Details of detachment*
1	1	0·94	C	Detachment operation 3 months previously
2	1	0·99	A→B	Aphakia
3	1	0 91	A	
4	1	0·69	C	
5	1	0·66	B	
6	1	1·45	C	
7	2	1·20	B	
8	2	1·24	C	
9	4	0·39	A	
10	4	1·22	A	Re-operation on Case 9
11	4	1·17	A	Aphakia
12	4	1·0	B	
13	4	Not done	C	
14	4	0·57	A→B	Aphakia
15	4	Not done	B	
16	8	0·79	A→B	Diathermy 5 yrs previously
17	8	0·92	B	
18	8	0·56	A	
19	8	0·84	A	Re-operation on Case 6
20	12	2 50	B	
21	12	1·70	A	
22	12	1·08	A	Diabetic traction detachment No holes
23	14	0·75	A	Diabetic traction detachment Holes seen
24	14	1·72	A	No holes seen Dense lens opacities
25	20	0·94	B	Retinal dialysis
26	24	2·44	A	No holes seen Congenital cataracts
27	60	1·37	C	Retinoschisis
28	64	1·13	B	

Table III *Duration of detachment related to immunoelectrophoretic properties of subretinal fluid*

Duration of detachment (*wks*)	*Immunoelectrophoretic group* A		A–B		B		C	
	No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*
1–4 (15 cases)	4	26·7	2	13·3	4	26·7	5	33·3
8+ (12 cases)	7	58·3	1	8·3	4	33·3	0	0

(Cases 6 and 8). Similarly low total protein concentration may be associated with immunoelectrophoretic Group A (*e.g.* Cases 3, 9, 18, 19, and 23) or Group C (Cases 1 and 4).

(4) Two patients in the series were studied twice. Case 9 initially showed a low total protein concentration (0·39 g./100 ml.), but this had increased (1·22 g./100 ml.) when a second operation was performed 3 months later (Case 10); the immunoelectrophoretic group (Group A) was unchanged. Case 6 was operated on again 3 months later (Case 19), and whereas the total protein concentration had decreased from 1·45 to 0·84 g./100 ml. the immunoelectrophoretic grouping had changed from C to A.

(5) Case 27 showed retinoschisis. The total protein concentration was 1·13 g./100 ml. and few of the normal serum constituents were present on immunoelectrophoresis (Group C).

(6) Cases 22 and 23 showed diabetic detachments. Case 22 was a typical traction detachment and Case 23 had two small retinal holes in addition to the traction appearance. In both the subretinal fluid resembled normal serum (Group A).

(7) Cases 1, 10, and 19 were re-operations. The total protein concentration was not notably raised. In Case 1 (Group C) the retina had become flat with absorption of subretinal fluid after the previous operation and had become re-detached at a later date. In Cases 10 (Group A) and 19 (Group A) the subretinal fluid had not absorbed after the initial operation.

Discussion

The technique of immunoelectrophoresis used in this study shows that subretinal fluid tends to come to resemble normal serum more closely as the duration of the retinal detachment increases. IgM (M.wt 900,000) was not detected in any of the cases studied. Table IV shows the molecular weight of proteins found in subretinal fluid and their concentrations in normal serum as described by Dettelbach and Ritzman (1968) and Rowe (1970). The findings of the immunoelectrophoretic study suggests that the chorio-capillaris and Bruch's membrane vary in their permeability. The change in the nature of subretinal fluid as the duration of the detachment increases may be explained by an increasing permeability of the chorio-capillaris, as suggested by Heath and others (1926). The absence in all cases of IgM, which has a high molecular weight, indicates that the permeability of the capillary endothelium and of Bruch's membrane is limited even in long-standing and re-operated cases, thus in no case did the subretinal fluid have protein characteristics of a true exudate. A constant relationship between immunoelectrophoretic examination and total protein concentration was not found and it is felt that immunoelectrophoretic examination is a more reliable indicator of dysfunction of the choriocapillaris and Bruch's membrane than total protein concentration.

Table IV *Molecular weight of proteins in subretinal fluid and their concentrations in serum*

Proteins	*Molecular weight*	*Concentration in serum (mg./100 ml.)*
Albumin	69,000	3,500–4,500
α_1Antitrypsin	45,000	210– 500
Gc-globulin	50,800	40– 75
Haptoglobin	100,000	30– 190
Haemopexin	80,000	80– 100
Transferrin	90,000	230– 320
IgA	186,000	156– 294
IgG	150,000	853–1,463

Summary

In 28 specimens of subretinal fluid obtained from 26 patients the following observations were made:

(1) High total protein concentration levels are found in long-standing retinal detachments. This confirms the work of others.

(2) The technique of immunoelectrophoresis used in this study enabled a more detailed examination of subretinal fluid to be made than has previously been reported. Subretinal fluid comes to resemble normal serum more closely with increasing duration of the detachment. IgG and IgA were detected but IgM was absent. The findings support the theory of a limited semipermeability of the endothelium of the chorio-capillaris and of Bruch's membrane in patients with retinal detachments.

(3) There is no apparent relationship between immunoelectrophoretic findings and total protein concentration estimations. It is suggested that immunoelectrophoretic examinations offer a more reliable indicator of chorio-capillaris dysfunction than do total protein concentration estimations.

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Prevention of vitreous loss

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Retrobulbar anaesthesia, digital massage, osmotic therapy, and acetazolamide are frequently employed in various combinations to effect ocular hypotony before cataract extraction.* It is believed by many that hypotony prevents vitreous loss during this operation.†

Profound akinesia to preclude extraocular muscle contraction and resulting shortening of the scleral shell is a clinically accepted mechanism to prevent vitreous loss (Kornblueth, Jampolsky, Tambler, and Marg, 1960). Another clinical and laboratory-proved method is the induction of acute hyperosmolarity.‡

Though digital massage induces immediate vitreous weight reduction in the closed rabbit eye, recent investigations have demonstrated a rebound phenomenon which increases both vitreous weight and intraocular pressure approximately 5 to 10 min. after the completion of massage (Obstbaum, Robbins, Best, and Galin, 1971). This time sequence would, of course, be totally undesirable during a lens extraction.

Experiments concerning the effects of hyperosmolarity and digital massage have been carried out on the closed eye which, though of significant clinical importance, is not comparable to an eye undergoing lens extraction. Consequently, this investigation was undertaken to evaluate the effects of digital massage and 20 per cent. mannitol infusion on vitreous weights in rabbit eyes that had undergone the initial steps of lens extraction.

Materials and methods

New Zealand albino rabbits weighing 3 to 5 kg. were used. General anaesthesia was induced with intravenous sodium pentobarbital, 30 mg./kg. Intraocular pressures were determined by Schiotz tonometry with the 5·5 g. weight, calibrated for the rabbit eye (Best, Pola, Blumenthal, and Galin, 1970). Vitreous body weights were measured by the use of a freezing technique detailed elsewhere (Robbins and Galin, 1969). In summary, the technique involves rapid enucleation of the eye, freezing it for 24 hrs in dry ice at −78°C., isolating the frozen spheroid of vitreous by careful dissection, and then weighing the isolated, intact frozen vitreous body to milligramme accuracy.

Ten animals received no therapy. After each had been anaesthetized for 15 min., intraocular pressures were measured bilaterally. In all cases, the pressures were normal and essentially equal. Both eyes were then enucleated rapidly and placed in the dry ice freezer. Vitreous isolation and weighing were performed 24 hrs later.

Fifteen rabbits were subjected to uniocular limbal incisions of approximately 60° after baselines had been established as in the controls. The posterior lip of the incision was depressed for 10 sec.

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*Atkinson (1943), Kirsch and Steinman (1955), Agarwal, Gupta, and Malik (1959), Friedman, Byron, and Turtz (1962), Hill (1964), Jaffe and Light (1965).

†Gartner (1959), Townes (1965), Jaffe (1968).

‡Kornblueth and Gombos (1962), Seeger and Lewis (1964), Robbins and Galin (1969).

every minute so that the anterior chamber was totally evacuated. After five min. the incision was frozen closed with dry ice (Figure) and both eyes were enucleated. Similar experiments were conducted in other groups of animals leaving the eye open for 7·5 min. and for 10 min.

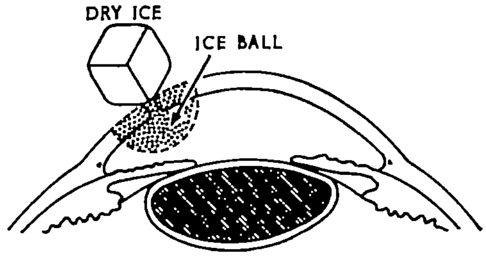

FIGURE *Diagram of closure of incision with dry ice*

Digital massage was carried out in a group of fifteen rabbits in which compression was maintained for 30-sec. intervals and released for 2-sec. intervals for a period of 5·5 min. Five min. later a limbal incision of 60° was made, and the eye treated as previously indicated. At the end of 5 min. the eyes were enucleated.

Fifteen animals received rapid infusions of 20 per cent. mannitol, 2 g./kg. Before the infusion one eye was enucleated and 60 min. after the termination of infusion, a 60° limbal incision was made in the remaining eye which was handled as above. After the eye had been open for 5 min. it was enucleated.

Results

Table I lists the vitreous weights in control animals. It is clear that the weights are close enough to permit the utilization of the unmanipulated eye as a control.

Table I *Vitreous weights in undisturbed animal*

Rabbit No.	*Vitreous weight (g.)*		*Per cent. variation**
	In untreated left eye	*In untreated right eye*	
1	1·654	1·649	0·30
2	2 072	2·068	0·19
3	1·893	1·896	0·16
4	1·860	1·855	0·27
5	1·778	1·780	0·11
6	1·586	1·582	0·25
7.	1·827	1·826	0·05
8	1·985	1·991	0·30
9	1·631	1 640	0·55
10	2·009	2·007	0·10

*Average weight variation = 0·23 per cent.

Table II *Vitreous weight change 5 min. after eye has been open for 5 min.*

Rabbit No.	*Vitreous weight (g.)*		*Per cent. weight loss in 5 min.**
	Control eye	*Opened eye*	
1	1·848	1·738	5·95
2	1·532	1·440	6·01
3	1·460	1·388	4·93
4	1·947	1·756	9·80
5	1·810	1·692	6·52
6	1·718	1·629	5·18
7	1·686	1·583	6·13
8	1·617	1·499	7·29
9	1·724	1·596	7·44
10	1·873	1·794	4·22
11	1·928	1·785	7·41
12	2·226	2·044	8·19
13	1·708	1·602	6·20
14	1·605	1·491	7·12
15	1·822	1·702	6·59

*Average weight loss in opened eye = 6·60 per cent.

Tables II to IV list the vitreous weights of non-manipulated, limbally incised globes. It is apparent that a significant loss of vitreous weight is caused simply by opening the eye.

Table III *Vitreous weight change* 7·5 *min. after eye has been open for* 5 *min.*

Rabbit No.	*Vitreous weight (g.)*		*Per cent. weight loss in* 7·5 *min.**
	Control eye	*Opened eye*	
1	1·837	1·719	6·41
2	1·549	1·440	7·03
3	1·587	1·487	6·29
4	1·624	1·518	6·53
5	1·925	1·772	7·96
6	1·748	1·622	7·20
7	1·656	1·555	6·10
8	1·483	1·385	6·62
9	1·598	1·478	7·50
10	1·870	1·739	7·01
11	1·819	1·683	7·47
12	1·728	1·624	6·01
13	1·608	1·524	5·22
14	1·451	1·349	7·03
15	1·964	1·782	9·27

*Average weight loss in opened eye = 6·91 per cent.

Table IV *Vitreous weight change* 10 *min. after eye has been open for* 5 *min.*

Rabbit No.	*Vitreous weight (g.)*		*Per cent. weight loss in* 10 *min.**
	Control eye	*Opened eye*	
1	1·866	1·773	4·98
2	1·811	1·680	7·24
3	1·439	1·300	9·65
4	1·647	1·542	6·36
5	1·572	1·422	9·55
6	1·948	1·807	7·23
7	1·708	1·611	5·67
8	1·781	1·656	7·02
9	1·645	1·522	7·45
10	1·916	1·817	5·15
11	1·763	1·632	7·44
12	1·464	1·359	7·19
13	1·627	1·469	9·69
14	1·794	1·654	7·82
15	1·878	1·746	7·02

*Average weight loss in opened eye = 7·30 per cent.

This reduction was not much altered by increasing the length of time that the eye was open before the globe was enucleated. As is shown in Table V, the vitreous weight change was essentially unaltered by previous digital massage for 5 min., even though intraocular pressure was substantially lowered at the time of surgery.

Table V *Vitreous weight change* 5 *min. after eye has been opened, having been massaged for* 5 *min.*

Rabbit no.	*Vitreous weight (g.)*		*Intraocular pressure in treated eye (Scale units Schiotz tonometer,* 5·5 *g.)*			*Per cent. weight loss in treated eye*
	Control eye	*Massaged* 5·5 *min. and opened* 5 *min.*	*Before massage*	*After* 5·5 *min. massage*	5 *min. after massage*	
1	1·403	1·309	3·0	16·0	8·0	6·71
2	1·484	1·378	4·5	20·0	8·0	7·15
3	2·049	1·912	4·0	19·0	10·0	6·68
4	1·465	1·347	3·0	17·0	9·0	8·05
5	1·553	1·442	3·5	14·0	7·0	7·16
6	1·630	1·527	2·5	13·5	7·5	6·32
7	1·618	1·524	4·0	18·0	10·5	5·82
8	2·009	1·848	3·0	15·0	9·0	8·01
9	1·902	1·773	4·5	16·0	9·0	6·79
10	1·811	1·691	3·0	14·0	8·5	6·64
11	1·914	1·813	3·5	15·5	7·5	5·28
12	1·907	1·767	2·5	12·0	6·5	7·35
13	1·923	1·762	4·0	13·0	8·0	8·36
14	2·183	2·001	3·0	14·0	7·5	8·34
15	1·696	1·572	3·5	13·0	6·0	7·32

*Average weight loss in treated eye = 7·07 per cent.

Table VI indicates that osmotic therapy produces a net reduction in vitreous weight significantly greater than that induced by atmospheric equilibration alone or by digital massage.

Table VI *Vitreous weight change* 5 *min. after eye has been opened, having been infused with mannitol* 60 *min. before being opened.*

Rabbit no.	*Vitreous weight (g.)*		*Intraocular pressure changes in treated eye (Scale units Schiötz tonometer,* 5·5 *g.)*		*Per cent. weight loss in treated eye*
	Control eye	*In eye treated with mannitol* 60 *min. and opened* 5 *min.*	*Before mannitol*	60 *min. after mannitol infusion*	
1	2·228	2·001	3·0	11·0	10·18
2	2·037	1·833	4·0	13·0	10·00
3	1·618	1·472	3·5	9·5	9·01
4	1·821	1·668	4·0	10·5	8·40
5	1·498	1·366	2·5	11·0	8·80
6	1·885	1·707	3·0	10·5	9·44
7	1·421	1·314	4·5	12·0	7·54
8	1·264	1·142	3·0	11·0	9·65
9	1·226	1·121	2·5	9·0	8·56
10	1·527	1·387	4·0	13·0	9·15
11	1·376	1·280	3·5	9·0	6·96
12	1·358	1·236	3·5	12·0	8·98
13	2·170	1·986	4·0	10·0	8·48
14	1·781	1·601	4·5	12·5	10·12
15	1·845	1·664	3·5	14·0	9·82

*Average weight loss in treated eye = 9·01 per cent.

Discussion

It is commonly believed that steps to produce hypotony are of benefit in the performance of intraocular surgery by reducing the incidence of vitreous loss (Gartner, 1959; Townes, 1965; Jaffe, 1968). It has never been shown, however, that hypotony is of value *per se*. This study would infer that hypotony *per se* is not of benefit in reducing the potential for vitreous loss, but is only a concomitant of techniques that are effective in reducing vitreous mass.

Once the eye is open, intraocular pressure is equilibrated with atmospheric pressure. In this state, any positive pressure against the globe will prolapse the vitreous body forwards. Vitreous prolapse may be (Gartner, 1959) similarly effected by collapse of the scleral shell, contraction of extraocular muscles, or internal expansion of the choroidal or subchoroidal spaces. If less vitreous is present, a margin of volume displacement becomes available to offset small vectors directed towards expelling the vitreous. It is certainly not the intraocular pressure (or hypotony) *per se* that is involved.

These studies indicate that vitreous water loss is caused simply by opening the eye. Most investigators are familiar with the observation that the entire rabbit lens and vitreous body is readily removed and will "drip water", if supported in air. This has also been demonstrated in eye-bank eyes (Irvine, 1953). Presumably, the closed space pressure gradient in the undisturbed eye is one factor in maintaining vitreous mass which is lost when the eye is opened. These data further show that previous digital massage does not induce a reduction in vitreous mass during the usual duration of time associated with removing the lens. In fact, in the rabbit, massage may induce vitreous weight rebound. This has been observed in the closed eye and, though the net vitreous weight change was not found to be increased after massage when it was studied in the open eye, the technique of this investigation does not preclude this phenomenon (Obstbaum and others, 1971).

The hyperosmolar state does appear to reduce vitreous mass even when the eye has been opened. Presumably, the osmotic gradient is operative during the usual time necessary for a lens extraction.

These data strongly support the idea of the clinical value of hyperosmolar therapy, but they cast doubt on the value of preoperative massage in decreasing vitreous loss. If this latter technique is of value, its effect is probably due to the dissemination of anaesthesia and the consequent improvement in akinesia (Atkinson, 1943; Gartner, 1959, 1961).

It is a fair observation that vitreous will not run uphill. Something pushes it out. Hyperosmolar therapy provides a theoretical margin of safety while digital massage does not (Robbins, and Galin, 1969). Of course, this margin of safety is theoretical, since the choroidal volume has not been measured in the open eye and may significantly reduce or totally offset any reduction in vitreous mass.

All in all, these studies tend to support the concept that, of all the available means to preclude vitreous loss, excellent akinesia seems most significant.

Summary

Limbal incisions were made in rabbit eyes to mirror the initial steps of lens extraction. The vitreous body loses water when the eye is open and decreases in weight. Previous digital massage does not increase this vitreous weight change but hyperosmolar therapy does.

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Response to mydriatics in the African

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It is common clinical experience that the pupil in the African dilates slowly in response to mydriatics. Full mydriasis can be obtained in about 40 minutes in the Asian or European, but takes much longer in the African. This difference in response has been observed in the same clinic at the same time and using the same drug. Scott (1945) noted the need for stronger mydriatics to dilate the pupil in Negroes. There must be an intrinsic peculiarity in the African iris, and it has been shown that this is not due to faulty innervation (Scott, 1945).

An obvious peculiarity of the African iris is the abundant pigmentation. The present study has revealed that the relatively slower response of the pupil to mydriatics in the African is indeed related to pigmentation, and that the pupil in the albino African behaves differently. The exact mechanism by which pigmentation influences mydriasis is not clear, and anatomical and physiological studies have been carried out in an attempt to find a possible explanation.

Methods

(a) The rate of dilation of the pupil was compared in Africans, Europeans, and albino Africans, using homatropine 4 per cent. and phenylephrine 4 per cent. The subjects were studied in the same room in the same natural daylight. Phenylephrine was instilled into the right conjunctival sac and homatropine into the left conjunctival sac in all cases. An equal number of drops was instilled from the same bottle and the diameter of the pupil was measured at 10-min. intervals using a ruler.

(b) Comparative biomicroscopical studies were made on the African, European, and albino African irides.

(c) A comparative histological study was made on the African and European irides.

Results

(*a*) *Dilation of the pupil*

Full mydriasis was obtained after about 40 minutes in the Europeans, but in the dark-skinned Africans dilation to the same extent could not be obtained even after 60 minutes. In the albino Africans dilation of the pupil was most brisk. There was no difference between the sexes, but dilation was a little slower in the older age group. Dilation started within 5 minutes in the Europeans and albino Africans, but in the dark Africans it started after about 10 minutes. Mydriasis started earlier with homatropine, but the degree of dilation was about the same with both drugs after 30 to 40 minutes. In the dark Africans the effectiveness of both drugs was reduced in the same proportion in that the final degree of dilation was the same. The results are shown in the Table (opposite) and in Fig. 1 (overleaf).

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Table *Dilation of pupil at* 10-*min. intervals. Diameter of the pupil* (*lower figures in each column are those of the left pupil*)

Race	Age (yrs)	Sex	Pupillary diameter (mm.)						
			Initial	Time (min.)					
				10	20	30	40	50	60
Dark African	24	M	3	3	3	4	6	7	8
			3	3	4	5	6	7	8
	31	M	3	3	3	4	5	6	6
			3	3	3	4	5	5	6
	17	M	3	3	3	4	4	5	6
			3	3	4	5	6	6	7
	30	F	3	3	3	4	5	6	7
			3	3	4	4	4	5	5
	26	F	2	2	3	3	4	5	7
			2	3	4	4	5	5	6
	17	M	3	3	3	3	4	4	6
			3	3	4	4	5	5	6
	30	F	2	2	2	3	6	7	8
			2	2	4	4	5	5	6
	31	M	2	2	3	5	5	6	6
			2	3	4	6	6	6	6
	65	M	2	2	3	3	4	4	5
			2	2	4	5	5	6	6
	45	F	2	2	3	4	6	7	7
			2	2	4	4	4	4	5
	37	F	2	2	3	4	4	5	7
			2	2	4	5	5	6	6
	24	M	2	2	2	2	3	3	4
			2	2	3	4	5	5	5
	43	M	2	2	3	4	5	6	6
			2	2	3	4	5	6	6
	35	M	2	2	3	5	6	6	6
			2	2	4	6	7	7	7
	Mean		2·36	2·43	3·32	4·14	5·00	5·54	6·21
Albino African	12	F	3	3	4	5	6	6	
			3	5	7	8	8	8	
	23	F	2	3	6	8	9		
			2	3	6	8	9		
	8	F	3	3	4	6	8	9	
			3	4	7	8	9	9	
	41	M	—	—	—	—	—	—	
			3	4	5	6	7	7	
	Mean		2·71	3·57	5·57	7·00	8·00	7·8	
European	31	M	2	3	4	6	8		
			2	4	6	7	9		
	54	M	3	4	5	6			
			3	5	6	7			
	49	M	2	3	4	6	7		
			2	4	5	6	7		
	52	M	2	3	4	5	6		
			2	4	5	6	7		
	30	F	3	4	5	7	7	8	
			3	5	7	8	9	9	
	Mean		2·40	3·90	5·10	6·40	7·50	8·5	

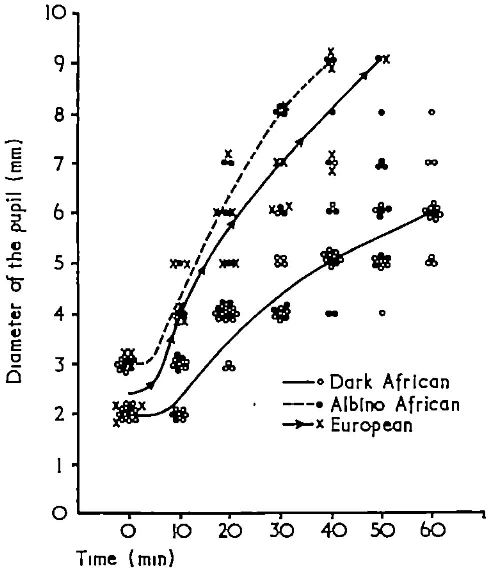

FIG. 1 *Rate of dilation of the pupil by 4 per cent. homatropine in European, African, and albino African*

(*b*) *Biomicroscopic appearance of the irides*

There are striking differences in the appearance of African and European irides. The anterior surface of the African iris appears as a dense, opaque, brown "moss carpet", and is characterized by a paucity of surface markings. Its radial trabecular pattern is often not seen except near the pupillary border, and the collarette, which divides the iris into the ciliary and pupillary portions, is sometimes not apparent. The crypts are few and small and look like small pits near the pupillary border, while the peripheral pits of Fuchs appear as pinpoints.

In contrast, the European iris has a wealth of surface detail. Its anterior surface looks more porous. The radial trabecular lines are well marked and the collarette can always be identified. Numerous large crypts are present.

In the albino African these surface markings are even more obvious, with an apparent lack of pigment.

(*c*) *Histological differences between European and African irides*

The histology of the iris in the two races is basically the same, but the anterior border layer in the African iris is much thicker and more pigmented. All the pigment cells contain large quantities of pigment. The stroma of the African iris contains more abundant branching pigment cells. The sphincter pupillae and the dilator pupillae and the posterior pigment epithelium do not appear to differ in the two races.

It is unreliable to compare the thickness of the irides from histological section as this depends upon the size of the pupil and other factors, but the impression is that the African iris may be thicker (Figs 2 to 5, opposite).

Discussion

The rate of dilation of the pupil is determined partly by the rate of absorption of the mydriatic. A large proportion of a drug instilled into the conjunctival sac is absorbed through the cornea into the aqueous humour. Systemic absorption probably has little

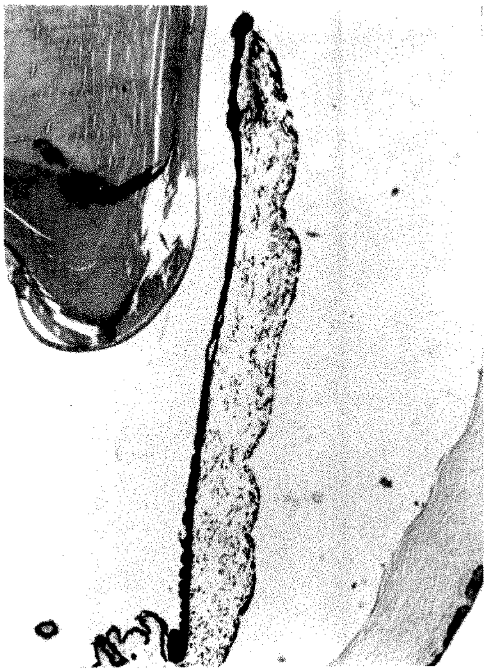

FIG. 2 *Photomicrograph of African iris.* ×23

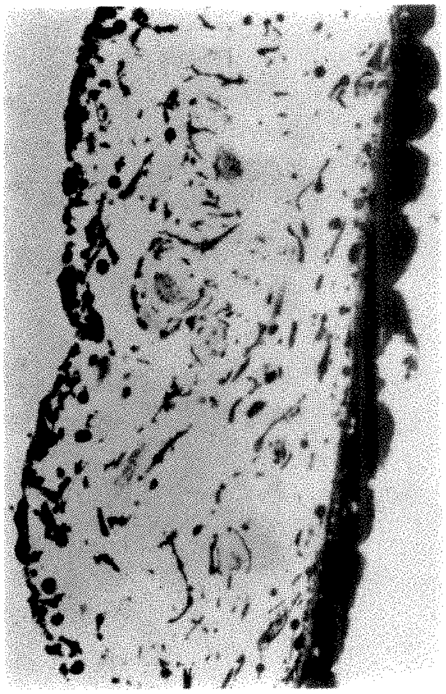

FIG. 3 *Same African iris near the root.* ×115

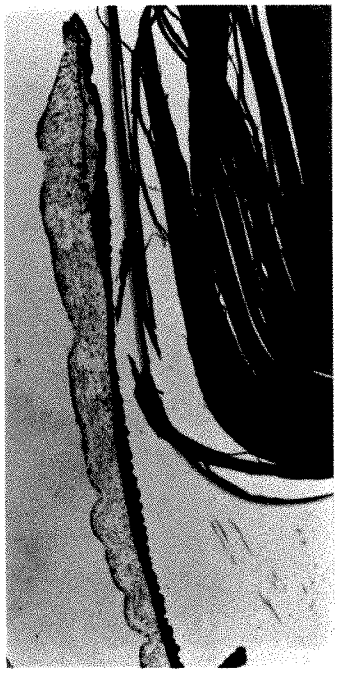

FIG. 4 *Photomicrograph of European iris.* ×23

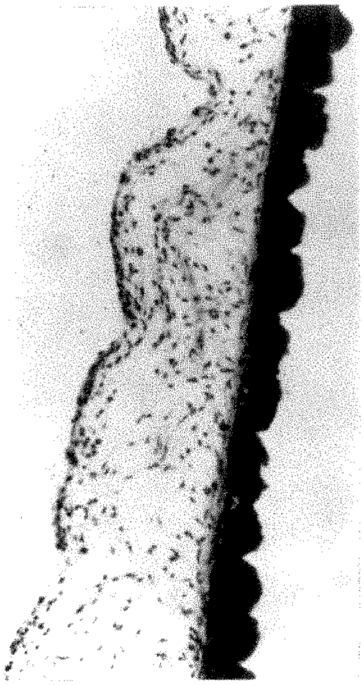

FIG. 5 *Same European iris near the root.* ×115

effect on the iris. From the aqueous humour the drug is absorbed by the iris surface. Gregersen (1960) has demonstrated that, in addition to the crypts, there are iris pores between cells in the anterior border layer. These openings communicate with tissue spaces within the iris stroma, which consist of clefts of Fuchs and tubular spaces surrounding the endothelial cells of the iris vessels (Gregersen, 1959). There is therefore a definite channel-system within the iris stroma through which aqueous humour passes freely in and out through the iris pores and crypts. In the African, the anterior border layer of the iris is thicker with denser iris chromatophores and has fewer crypts. It is also probable that there is more stroma within the iris and hence fewer tissue channels. The absorption of a mydriatic from the aqueous fluid would be much slower than in an iris with more numerous and larger crypts and pores. Thus the onset of mydriasis starts later in the dark African iris.

The effect of phenylephrine, which acts on the dilator pupillae muscle, occurred later than that of homatropine, which acts on the more superficial sphincter pupillae muscle. Phenylephrine has to traverse a much longer distance through the tissue spaces. The response to adrenergic stimulators is thus more delayed than that of cholinergic blocking agents. Once absorption had taken place the effect of both drugs appeared to be the same.

Comparison of histological features may not give reliable results. Individual variations in the architecture of the iris of any given eye are so unique that they have led to the cults of "irido-diagnosis" and "oculo-diagnosis". The thickness of the iris, for instance, varies according to the degree of dilation of the pupil. Immediately before death, the pupil dilates, but after death it gradually decreases in size to an average diameter of about 3·5 mm. Fixatives diminish the size of the pupil still further to about 2 to 3 mm. (Duke-Elder and Wybar, 1961). It has also been shown that there is considerable individual variation in the thickness of the iris. The average thickness when the pupil is semi-dilated is 0·3 to 0·6 mm. at the collarette and 0·05 mm. at the iris root. Although reliable comparative values cannot therefore be given, biomicroscopic study leaves the impression that the African iris is more compact, with possibly more stroma. This is further borne out by the frequent observation that iridodonesis is less common in aphakia in the African. It is also possible, as it has been noted before (McNair, 1951), that the dark iris is thicker than the light iris.

If the African iris is thicker and more compact, it would be less easily compressed, and this would partly explain its sluggish dilation, in that it may not be able to exert as much force as a lightly-pigmented iris is able to develop. Mapstone (1968) made a mathematical analysis of the mechanics of pupillary block in closed-angle glaucoma, which demonstrated the various forces exerted by the iris as the pupil dilated. These forces may be different in the African and could perhaps explain the rarity of acute closed-angle glaucoma in the African. Further study of this feature seems to be indicated.

Summary

The dark African pupil dilates more slowly in response to a mydriatic than that of the lighter-skinned races or albino Africans. This difference seems to be related to the deeper pigmentation and more compact architecture of the dark African iris, with fewer tissue channels. It is possible that the African iris may not be able to exert the force which may lead to pupillary block, such as lightly-pigmented iris is able to develop.

I should like to acknowledge the useful suggestions which I have received from Prof. E. S. Perkins, Institute of Ophthalmology, London, and to thank Prof. N. Ashton, Department of Pathology, Institute of Ophthalmology, London, for supplying a specimen of European iris.

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Brit. J. Ophthal. (1971) 55, 544

Liberation of iris pigment in the anterior chamber

After instillation of 10 per cent. phenylephrine hydrochloride solution

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Phenylephrine hydrochloride is a topical mydriatic widely used in clinical practice. Its action is due to a direct sympathomimetic effect upon the myoneural junction, resulting in mydriasis, slight cycloplegia, an increase in the facility of aqueous outflow, and constriction of the conjunctival vessels. The 10 per cent. aqueous solution is commonly used, but reaction has been observed after the instillation of solutions as weak as 0·125 per cent. (Havener, 1966) and 0·1 per cent. (Haddad, Moyer, and Riley, 1970), which is enhanced by increased absorption after trauma to the corneal epithelium. One side-effect of its action is the liberation of pigment granules into the aqueous 30 to 40 minutes after instillation, a phenomenon first described by Mitsui and Takagi (1961), who observed that it occurred in 4·6 per cent. of subjects after the instillation of a 5 per cent. solution. The majority of these subjects were middle-aged or elderly, and it was shown that the pigment granules had the same characteristics as those in the cells of the iris neuroepithelium. Haddad and others (1970) observed similar aqueous floaters in a high proportion of subjects over the age of 50 years after the instillation of 1 per cent. and commercial 10 per cent. solutions Biggs, Alpern, and Bennett (1959) observed similar floaters after the subconjunctival injection of epinephrine, and Chamlin (1959) observed them in cases of papillitis and drew attention to the diagnostic confusion which may follow the instillation of mydriatics in these cases.

The present study was begun after the frequent chance observation of aqueous floaters in eyes into which 10 per cent. phenylephrine hydrochloride drops had been instilled before routine fundus examination. During a period of two months, 150 patients were examined biomicroscopically both before and after dilatation of the pupils with 10 per cent. phenylephrine hydrochloride solution.

In forty cases (27 per cent.) an aqueous flare and floaters were observed after dilatation of the pupils; in some cases "Novesine" (Benoxinate hydrochloride 0·4 per cent.) had also been instilled.

Method

(1) PRELIMINARY STUDY

A random selection of 150 patients (73 males and 77 females) ranging in age from 12 to 86 years attending routine Out-patient Clinics had mydriatics instilled into both eyes before ophthalmoscopy.

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A 10 per cent. solution of phenylephrine hydrochloride B.P. in sterile aqueous solution, with benzalkonium chloride B.P. 0·04 per cent. as antiseptic, was instilled once into both eyes of each patient; cases of suspected optic neuritis, diabetes, uveitis in any form, and those with abnormal anterior segments were excluded from the study.

Of the 150 patients studied, forty (27 per cent.) between the ages of 43 and 86 were found to have developed an aqueous flare and floaters in both eyes. Patients exhibiting occasional floaters were not re-examined. No floaters were seen in any of the patients between the ages of 12 and 43 years. These results are summarized in Fig. 1.

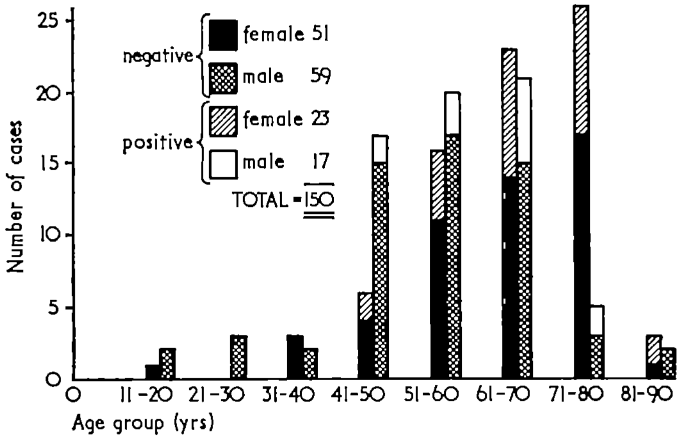


FIG. 1 *Age and sex distribution of 150 patients examined after instillation of phenylephrine hydrochloride. Those who exhibited pigment liberation are shown as positive*

Table I *Age and sex distribution of forty patients showing pigment liberation after instillation of 10 per cent. phenylephrine hydrochloride*

Age (yrs)	*Male*	*Female*	*Total*
41–50	2	2	4
51–60	3	5	8
61–70	6	9	15
71–80	2	9	11
81–90	–	2	2
Total	13	27	40

(2) DETAILED STUDY OF PIGMENT LIBERATION

The forty patients in whom pigment liberation had been observed were recalled for more detailed examination to determine whether any common factor other than age could be found. The age and sex distribution is shown in Table I. 10 per cent. phenylephrine hydrochloride drops were instilled into both eyes three times at 5-min. intervals.

Pigment liberation was seen to start 30 to 45 minutes after the first instillation of drops, reaching a maximum 1 to 2 hours after instillation, and gradually disappearing after 24 hours.

In each case the following details were noted: age, sex, iris colour, and intraocular pressure and gonioscopic appearances before and after dilatation of the pupil. 1½ hours after the pupil had become fully dilated (with liberation of pigment) 4 per cent. pilocarpine nitrate drops were instilled into each eye, and the eyes were re-examined when the pupils had become constricted.

Results

IRIS COLOUR

The main iris colour was noted and classified by the categories described by Riddell (1942). The results are shown in Table II.

Table II *Distribution of iris colour (Riddell, 1942)*

Colour	*No. of patients*
1 Blue	10 (6 male, 4 female)
2 Grey	10 (6 male, 4 female)
3 Green	6 (6 female)
4 Yellow	None
5 Tan	14 (1 male, 13 female)
6 Chocolate	None

Table III *Range of fall in intraocular pressure in thirty cases*

Fall in intraocular pressure (mm.Hg)	*No. of cases*
0– 5	20
5–10	8
10–15	1
15–20	1

INTRAOCULAR PRESSURE

In six patients there was no change in intraocular pressure in response to 10 per cent. phenylephrine hydrochloride.

Of the remaining 34, thirty showed a fall (Table III), the maximum being 19 mm.Hg, and four showed a rise.

Of the four cases showing a rise, three rose by only 1 to 3 mm.Hg; the quantity of pigment liberated into the anterior chamber in these cases was not significantly greater than that observed in the cases showing a fall in pressure.

The one remaining case was that of a 71-year-old woman with occlusion of a retinal tributary vein, who was found to have chronic simple glaucoma (gonioscopy showed Grade 0–1 angles). In this case there was a rise in intraocular pressure of 6 mm. in one eye and 11 mm. in the other.

GONIOSCOPY

Of the eighty eyes examined, nine showed an abnormally large amount of pigment in the angle before the instillation of phenylephrine. After dilatation of the pupils and liberation of pigment, no increase in the amount of pigment was seen in any case. In several cases the angle appeared to be wider after dilatation of the pupil than before.

IRIS PIGMENT LIBERATION

This was observed in all the eighty eyes examined, but varied in intensity. For ease of identification, three grades were devised, corresponding to grades 4, 5, and 6 of Mitsui's scale of floaters (1943).

+ A mixture of pigmented and non-pigmented floaters in one section of the slit-lamp beam. (10 cases).

++ Hundreds of pigmented floaters in one section of the slit-lamp beam, sometimes forming laminated patterns; these cases tended to overlap with the next grade (13 cases).

+++ Innumerable pigmented floaters in one section of the slit-lamp beam. Sometimes these were laminated and sometimes they took on the appearance of a pigmented veil or curtain (17 cases).

In some of the cases in the last group, the manner in which pigment was liberated took on certain distinct patterns.

(*i*) A cloud of pigmented floaters at the pupil margin (Figs 2 and 3)

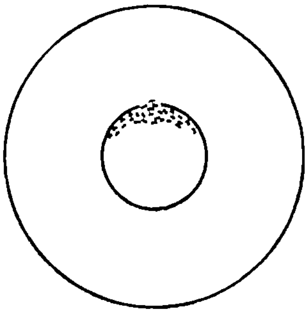


FIG. 2 *Liberated pigment first seen as a cloud of pigmented floaters emerging from the pupil margin*

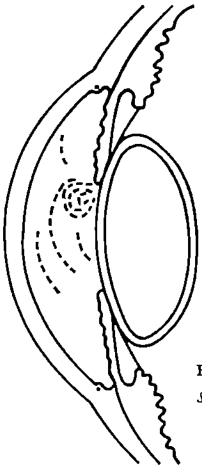
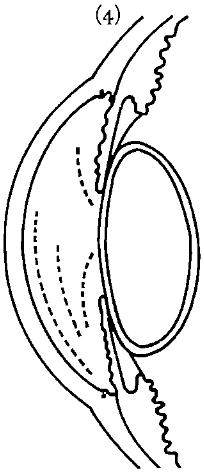


FIG. 3 *Lateral view of early stages of pigment liberation*

(*ii*) Laminae of floaters, most marked 1–2 mm. posterior to the corneal endothelium (Fig. 4)

(4)



(5)

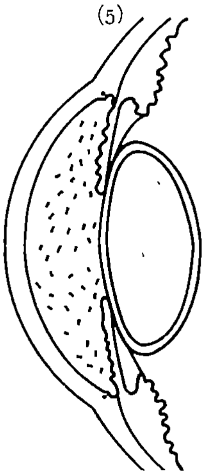


FIG. 4 *Liberated pigment takes the form of laminae closely related to the posterior corneal surface (lateral view)*

FIG. 5 *There is a faint flare in the anterior chamber, which is filled with innumerable pigmented floaters (lateral view)*

(*iii*) A faint flare and innumerable pigmented floaters filling the anterior chamber (Fig. 5)

(*iv*) A "curtain" of pigment particles across the pupil.

All these patterns were observed in different eyes; they were quite distinct from each other and there was no progression from one pattern to another.

RE-EXAMINATION

After constriction of the pupils with 4 per cent. pilocarpine nitrate solution, each patient was re-examined biomicroscopically. At this stage it was found that the amount of pigment liberated had increased still further. The pigment disappeared during the ensuing 24 hours.

Discussion

Pigment liberation into the anterior chamber after the instillation of mydriatics is a well-known phenomenon, and the findings of the present study confirm this, particularly in respect of phenylephrine hydrochloride. No significant discovery emerged from this study, except that the great majority of patients in which pigment liberation was observed were over 40 years old, which confirms the findings of other workers. The observation is of clinical importance, because phenylephrine is now widely used in ophthalmology and this pigment liberation may be confused with anterior uveitis or with a microscopic hyphaema. It is important, therefore, when contemplating the use of phenylephrine to examine the patient's eyes biomicroscopically before it is instilled to ascertain the presence or absence of aqueous floaters. If pigment liberation should occur afterwards, the fact should also be recorded as a warning to unwary future examiners. It is possible to distinguish mydriatic-induced floaters from those of iritis by careful examination; the former are larger and pigmented, whereas the latter are smaller and greyish in appearance. The patterns of pigment liberation are possibly related to variations in the viscosity of the aqueous, so that when this is increased (as in pattern *iii*) there is cessation of its circulatory stream. None of the patients examined experienced any symptoms from the presence of floaters and in all cases the floaters disappeared without any treatment; no evidence was found of the presence of free erythrocytes in the anterior chambers of any of the eyes examined.

The mechanism by which pigment granules are liberated is probably that postulated by Mitsui and Takagi (1961), *i.e.* they originate from degenerate cells of the pigment epithelium of the iris which rupture during contraction of the dilator pupillae. The degeneration of these cells is thought to be a senile change and angiosclerosis is a predisposing factor. The phenomenon of rebound miosis after phenylephrine mydriasis recently described by Haddad and others (1970) suggests that the dilator muscle may also be damaged and that this may be an additional source of floaters. The relatively high incidence of pigment liberation in the present study (27 per cent.) as compared with that found by Mitsui and Takagi (1961) may be the result of our having used a stronger solution of phenylephrine hydrochloride (10 per cent.), inducing a greater contraction of the dilator pupillae with more extensive cellular damage. The further increase of pigment liberation which followed the instillation of pilocarpine may be a mechanical effect of stretching the damaged epithelium.

Our observations are similar to those of previous workers, with one exception. No notable increase in trabecular pigmentation was found on gonioscopy after pigment liberation, and in some cases the width of the angle appeared to increase. In thirty of the cases examined, the usual fall in intraocular pressure was observed after the instillation of phenylephrine; the exact mechanism whereby this fall occurs remains unknown. In the one case of chronic simple glaucoma previously mentioned there was a rise in intraocular pressure, a rare occurrence which has previously been reported by Lee (1958) and Hill (1968). This paradoxical response may possibly be attributed to blockage of an already embarrassed trabecular meshwork by liberated pigment granules.

Summary

During a period of 2 months, 150 patients were examined after the instillation of 10 per cent. phenylephrine drops as a routine mydriatic before ophthalmoscopy. Forty of these (27 per cent.) were found to develop a flare and aqueous floaters 30 to 45 minutes later because of liberation of iris pigment; some showed characteristic patterns. No significant common factor was found except that all were over 40 years old and no symptoms were experienced. The effect of phenylephrine on the intraocular pressure and the angle were also noted. There is a danger of confusing this relatively harmless phenomenon with anterior uveitis; it is probably caused by damage to the iris pigment epithelium.

We wish to thank Mr. A. Hirtenstein, Mr. D. F. Woodhouse, Mr. B. R. Kesby, and Mr. A. W. Sollom for their advice and for allowing us to examine their patients, and Dr. M. Paul for his help with the illustrations.

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Simplified limbal approach in squint surgery

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The limbal approach is not new to squint surgery* but, despite its considerable advantages in exposure and subsequent healing, the methods described so far are not easy to perform to obtain the best final results. In particular, the incision commonly described needs very accurate suturing of the conjunctival flap with its two radially placed incisions to achieve a good cosmetic result. The method described below uses a triangular flap of conjunctiva which needs only a single limbal suture to restore limbal anatomy and is therefore much more easily performed.

Operative technique

The limbal fixation sutures (black nylon or Jameson Evans) are placed into episcleral tissue at 6 and 12 o'clock and the eye is pulled across laterally to allow access to the medial rectus. The insertion of the medial rectus may be readily identified beneath the conjunctiva and a horizontal conjunctival incision is made just above and parallel to the upper border of medial rectus, some 3 or 4 mm. from the limbus (Fig. 1, 1). Tenon's fascia is incised in the same plane and the wound is enlarged right up to the limbus in the 1 o'clock position. Tenon's fascia and conjunctiva are next cut away as one layer from the limbus, using non-pointed scissors, as far round as 5 o'clock. Lifting the combined Tenon's fascia and conjunctiva together, this triangular flap is dissected back, exposing the entire medial rectus insertion without any bleeding. It is important to take the limbal disinsertion of the conjunctiva as far round as 5 o'clock, otherwise excessive traction on the conjunctival flap for exposure of the muscle may tear the conjunctiva away from the limbus in a radial direction. The muscle insertion may then be moved or dealt with in whatever way is necessary (Fig. 1, 2).

When closing the conjunctiva, the apex of the triangular flap is identified and the flap held across its original site. It will almost invariably be found that if an apical suture were used then the conjunctiva would gape around the limbus. Holding the flap at the apex, it can readily be seen just where the suture must be placed along the originally limbal edge of the conjunctiva to ensure a snug fit around the limbus (Fig. 1, 3). The second bite of this suture into the conjunctiva superiorly must first penetrate episcleral tissue and then emerge through the conjunctiva close to its edge. A large bite of conjunctiva which misses episcleral tissue tends to pull a hood of conjunctiva across the limbus. Normally a second suture will be needed in the horizontal extension of the incision, but occasionally this will be superfluous.

When a recession–resection operation is being performed, it is often convenient to expose both horizontal muscles before finally deciding how much to adjust the position of the muscle insertions. This applies particularly to second operations on the same eye. Using the fixation sutures at 12 and 6 o'clock as shown facilitates this. In any case it is often convenient to leave the suturing of both conjunctival flaps until the end of the operation. The 12 o'clock fixation suture is used to pull the

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*Cortes (1962), Massin and Hudelo (1962), Moreno de Mulet (1964), von Noorden (1968, 1969) eye slightly downwards, giving full access to the superior limbus from either side. Fig. 1, 4 shows that, at the end of the operation, all four conjunctival sutures are beneath the upper lid and that no conjunctival scars are visible in the interpalpebral fissure. The limbal incision when healed is virtually undetectable.

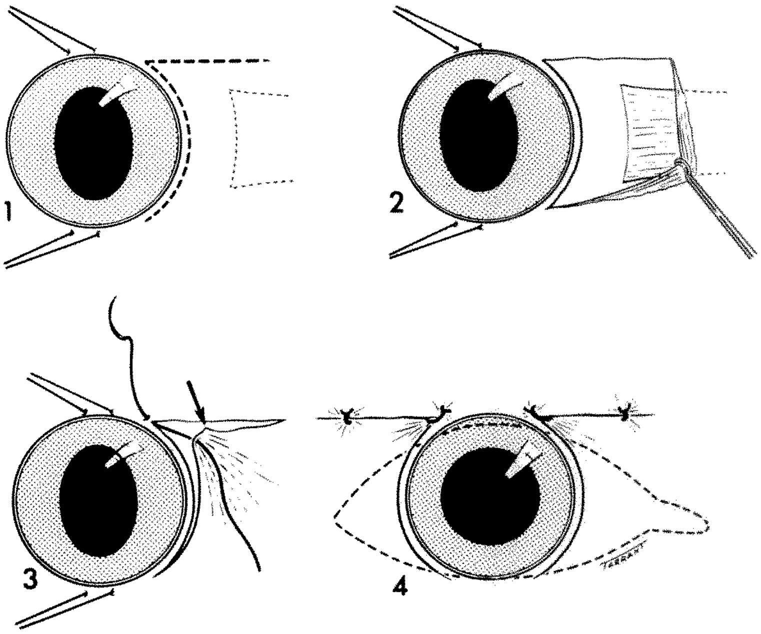

FIG. 1 *Steps in a right medial rectus recession operation*

(1) The faintly dotted line indicates the medial rectus beneath the conjunctiva. The heavily dashed line indicates the position and extent (1 to 5 o'clock) of the incision through conjunctiva and Tenon's fascia

(2) The flap of conjunctiva and Tenon's fascia allows full exposure of the medial rectus insertion. Note that extending the limbal incision far enough inferiorly prevents the conjunctiva from tearing away radially

(3) Suturing the conjunctival flap back. Note that the suture does not pass through the original apex of the flap (arrowed) but lower down the originally limbal edge to give an accurate limbal fit to the conjunctiva

(4) Final appearance after a recession-resection operation with four conjunctival sutures all lying beneath the normally opened upper lid. The dashed line indicates the interpalpebral aperture

Throughout a normal squint operation a 6–0 plain collagen suture is used. This allows for reattaching both muscles and for the conjunctival suturing. Because this suture is soluble and the conjunctival sutures are placed beneath the upper lid, the patient suffers the minimum of discomfort, and this method has proved very satisfactory in children and young adults.

This limbal approach is not used for vertical rectus muscle surgery, nor for oblique muscle operations as there is no virtue in bringing a well-hidden conjunctival wound into the interpalpebral opening.

The appearance of an operated eye 24 hours after a medial rectus recession is shown in Figs 2 and 3 (overleaf).

Summary

A method of approaching extraocular muscle surgery in cases of squint by way of the limbus is described and illustrated.

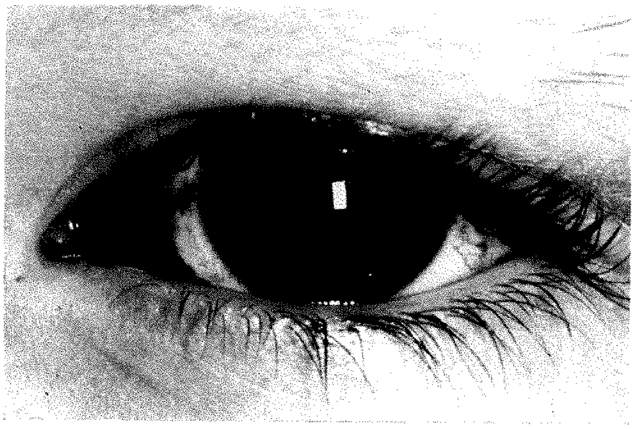

FIG. 2 *Left eye 24 hours after a medial rectus recession in a 5-year-old boy*

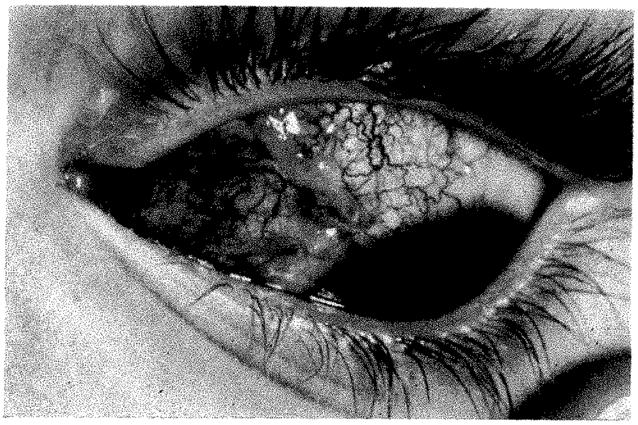

FIG. 3 *Same eye as in Fig. 2 looking down to show the sutured conjunctiva. There are two sutures with some mucus around them*

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Dictyoma

CARL H. IDE

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Badal and Lagrange (1892) were the first to describe a tumour of the ciliary body which they considered to be carcinoma. Other early reports of similar tumours of the ciliary body were given by Emanuel (1900), Verhoeff (1904), Kuthe and Ginsberg (1905), and Fuchs (1908). The latter suggested that the tumour be named "diktyoma" (derived from the Greek word "diktyon" for net) since it was composed of cells forming a net-like structure.

This case is presented because of the rarity of occurrence of the tumour. According to a detailed review of dictyomata by Andersen (1962) only 22 cases could be classified as such. Recent reports of cases of dictyoma have been given by Iwamoto, Witmer, and Landolt (1967), and Shivde, Asha Kher, and Junnarkar (1969).

Case report

A 4-year-old boy was seen in the Eye Clinic of the University of Missouri for evaluation of pain of 2 months' duration in his right eye. Within the past year, his parents had noticed a change in the colour of the iris of the right eye. There was no family history of ocular malignancies.

Examination

The visual acuity without correction was right eye 6/18 and left eye 6/6. Both pupils were round, but the right was larger than the left and was eccentrically located towards the 4 o'clock position. A greyish mass was seen through the pupil pushing the inferior nasal quadrant of the iris forward and penetrating the iris tissue. Slit-lamp examination revealed a moderate amount of rubeosis of the whole iris and peripheral anterior synechiae from 3 to 6 o'clock position. The ocular tension was 50·6 mm. Hg (Schiøtz) with the 10 g. weight in the right eye and 17·3 mm. Hg (Schiøtz) with the 5·5 g. weight in the left eye. Ophthalmoscopy with dilated pupil showed a large, elevated, white mass in the ciliary body at the 4 o'clock position. The clinical diagnosis of probable dictyoma was made.

Surgery

The right eye was enucleated.

Pathological findings

Macroscopic examination

Upon sectioning of the right globe a firm whitish tumour mass is noted in the region of the ciliary body (Fig. 1, overleaf). It measures approximately 1 cm. in its greatest dimension.

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(1)

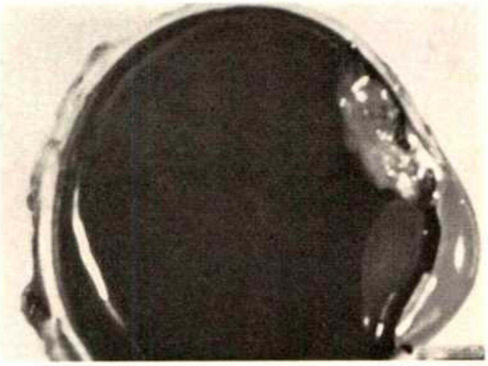

FIG. 1 *Section through globe, showing white mass involving ciliary body and iris*

(2)

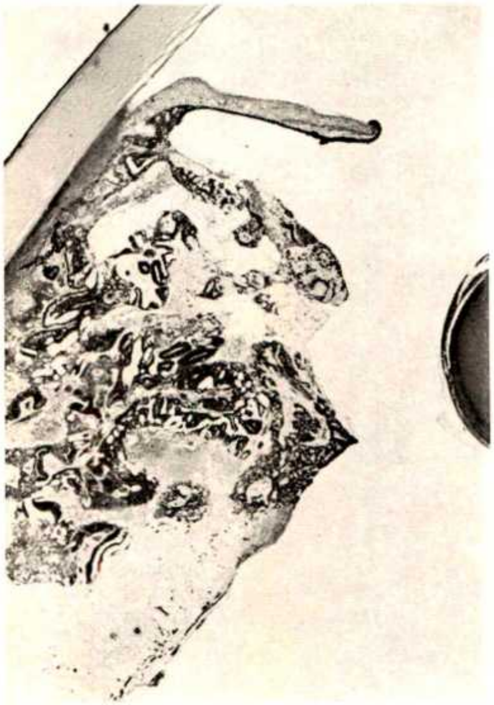

FIG. 2 *Tumour arising from area of ciliary body.* ×16

Microscopic examination

The tumour replaces the ciliary body and protrudes mainly into the posterior chamber (Fig. 2). Extension into the anterior chamber is also evident. Marked peripheral anterior synechiae are found. The tumour consists of tall columnar cells arranged in gland-like structures (Fig. 3).

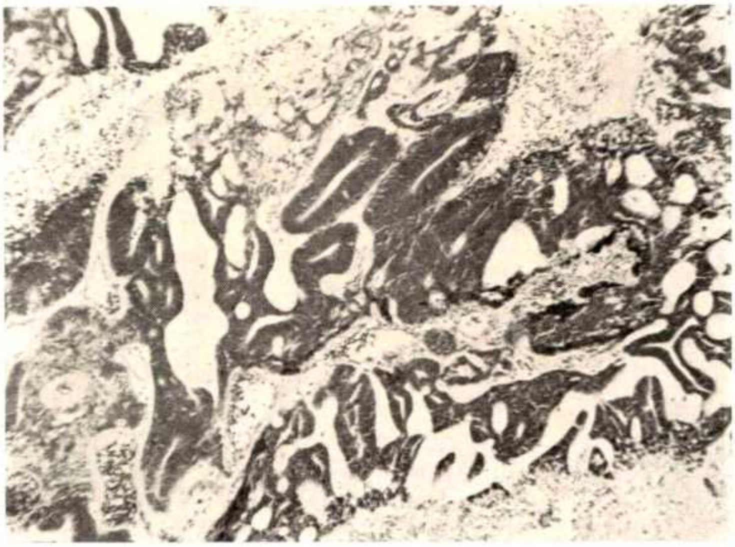

FIG. 3 *Enlargement of part of Fig. 2, showing structure of tissue consisting of tubular arrangement with cleft-like spaces.* ×52

These cells have elongated, hyperchromatic nuclei (Fig. 4, overleaf). Very little stroma is seen. Several cells contain a dark granular pigment. A considerable amount

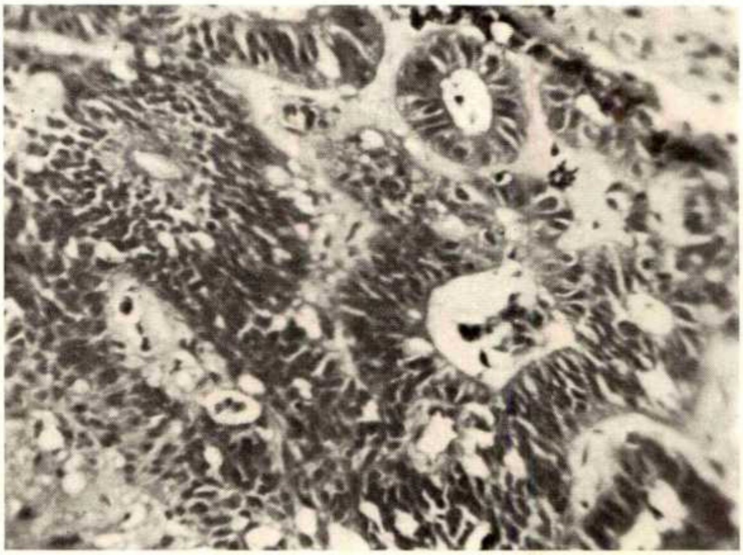

FIG. 4 *Portion of tumour with columnar cells forming rosettes.* ×218

of cupping of the optic disc and atrophy of the ganglion cell layer of the retina are noted.

The diagnosis of dictyoma with secondary glaucoma is confirmed histologically.

Discussion

Dictyomata are potentially malignant tumours originating from the pars ciliaris retinae. They have a tendency to grow as embryonic retinae. Little or no stromal tissue is found. Although the malignant behaviour of the tumour is noted by its infiltrating and destructive properties, no instance of metastasis has been seen (Reese, 1963).

Summary

A case of dictyoma with secondary glaucoma is reported. The tumour was detected clinically and the diagnosis verified by microscopical examination.

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Spontaneous orbital haemorrhage

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If one uses a title such as the above it is incumbent upon one to define exactly what it means. The purpose of this paper is to consider the occurrence of haemorrhage within the orbit not caused by local trauma and not referable, as far as can be ascertained, to any constitutional causative condition. Its justification consists in the rarity of the condition; in a long career the writer had had personal experience of only three cases. It is unfortunate that the notes of one of these three cases are not available; it was, however, identical in all essential details with the two to be presently described.

It is likely that a true spontaneous haemorrhage, using the phrase in the literal sense, never occurs. Even when the expression is used in the conventional sense, the occurrence is of extreme rarity, as Whitwell (1956) pointed out. He described the case of a 63-year-old woman, who suddenly developed a severe headache and right proptosis. No systemic abnormality was discovered, the orbit was evacuated of blood at operation, and recovery was rapid and complete. Whitwell quoted two similar cases, apparently truly spontaneous—the second case of Wheeler (1937) in a man of 45, and that of Roberts (1955) in a man of 25. Most, if not all, of the other cases to which he refers would appear to have some systemic cause to which the occurrence could be referred. Thus, Wharton Jones (1863) described the event in a young woman dying of uraemia and Priestley Smith (1888) a similar occurrence in a haemophiliac. Awerbach (1933) described two cases which he called spontaneous, but they were associated with scurvy and haemophilia respectively.

Birch-Hirschfeld (1930) reviewed the literature and reported one personal observation. His collection appeared to refer to cases associated with some causative general condition, such as haemophilia, scurvy, blood dyscrasia, renal and vascular disease, or some gynaecological or obstetrical event. Spanyol (1964) described an orbital haemorrhage without local trauma in a 46-year-old female; 1 ml. blood was aspirated from the orbit and vision was unharmed. He attributed the condition to preclimateric hormonal influences. Kubík (1963) described it in a 50-year-old man with moderate hypertension (200/100). Lijo-Pavía (1962) described a case in a 38-year-old man, which was unusual on account of the recurrence which the patient suffered. The blood coagulation time taken on the occasion of his first haemorrhage was 10 minutes. There were recurrences at intervals of 3 years, 5 years, and 11 years. The cause was said to be increased capillary permeability and metabolic disturbance affecting coagulation time.

The two patients here presented were similar in that they were both fit young men, and in each case the haemorrhage was at least preceded, if not actually caused, by moderate physical exertion which in such subjects would not ordinarily be looked upon as a potential cause of vascular catastrophe.

The first patient was in his early thirties and may truly be described as an athlete of unusual physical strength and fitness. In the preceding decade he had been an outstanding oarsman, and had taken part in this strenuous pursuit for years at regattas and in University rowing. For three successive

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years he rowed in the Oxford boat in their annual race against Cambridge. On leaving the University he took up rugby football, played for one of the most prominent clubs in the country, and was given a trial for the English team. His physical condition was therefore beyond reproach; he lived a very healthy life, and died in his seventies of carcinoma of the lung. At the time in question he was waiting in the boathouse, with the Oxford crew, for the moment to arrive when they should get into their boat and take to the water for the annual race against the sister University; the time of the year was, as usual, early spring; the weather was cold, and he was suitably clad as a spectator. Such a moment is charged with some tension and a nervous atmosphere is always apparent; by way of creating a diversion he walked into the gymnasium and, taking hold of the rings, did a slow turn and landed quietly on his feet. He immediately felt an impulse in his right orbit; his eye was rapidly and considerably displaced forwards, and he saw double. Despite his consternation he followed the race in the launch, overcoming the unusual embarrassment of seeing four crews by the simple expedient of covering the affected eye with his hand. When he consulted the writer that evening, the eye was found to be proptosed some 10 mm. and a little depressed; movements were limited, and diplopia was present in all positions of gaze. Knowing his past history I did not take too serious a view of his trouble; I told him that in a day or two he would have a "black eye", that the eye would gradually recede to its normal position, that his diplopia would disappear and ocular movements return to full, and that his sight would be unimpaired. All these prophecies were strictly fulfilled; I saw him seven times in the ensuing 30 years and noted no residual trouble from the occurrence at any time.

The other case was that of a young man in his late twenties, a resident medical officer in a London hospital, and son of one of the consultants. Again he was a perfectly fit type; before the occurrence he had had a mild infective hepatitis, but the serum bilirubin had returned to normal in a week. He was returning from a social occasion of a mildly convivial nature in his car, and leant over the back of the driving seat to retrieve a tool from under the back seat. He felt an impulse behind the right eye and took little notice of it; next morning the right eye was proptosed, there was a subconjunctival haemorrhage, and he saw double in all directions of gaze. The proptosis increased during the day; by the time I saw him at hospital considerable consternation had been caused to his father and colleagues as may be imagined, and many investigations were already in hand, including a full blood examination, skull *x* ray, etc., all of which in due course proved negative. Vision was unimpaired, but there was some discomfort on ocular movement. Mainly on account of his family background, I admitted him to hospital for a few days. The proptosis subsided slowly but not quite completely; diplopia was sometimes noticeable subsequently on ocular deviation when he was tired. Three years later the condition recurred in very similar but milder fashion, this time following an attack of vomiting. Recovery was complete in 2 days. It is interesting to note that in the interval between the two episodes the subject had done some flying with the Royal Auxiliary Air Force, including aerobatics, which sometimes involved subjection to "negative G" to the point of "red-out"; no harmful effects followed these experiences, and there was no residual effect other than that mentioned above in the subsequent 10 years.

Though in each of the cases described it is true that some exertion preceded the episodes, it is felt justified to describe them under the heading "spontaneous". It is interesting to speculate on the probable cause of such occurrences in healthy fit young men. Just as subarachnoid haemorrhage may occur unsuspected and unannounced in apparently fit people, often from a local congenital vascular weakness, so presumably could orbital haemorrhage. Opportunity is not provided for the investigation of such a possibility. Something of the kind may, and indeed must, be operative; if so, it is strange that the event does not occur more often. It is further difficult, on such a supposition, to account for the recurrences, and to explain why such episodes do not occur in other regions of the body. No great difficulty arises in considering the occurrence of orbital haemorrhage in the presence of predisposing general states, and the fact of exertion apparently being a factor in the two cases here described may provide some clue in the elucidation of an unusual condition.

Summary

Two cases are described of orbital haemorrhage occurring in fit young men after mild exertion. The relevant literature is reviewed. Attention is drawn to the frequent existence of a predisposing general state, and its absence in the cases described.

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Unusual causes of epiphora

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Most cases of epiphora are accepted as being due either to trauma, in which case there is usually a relevant history, or to stenosis of the nasolacrimal duct following some vague inflammatory process. The following cases are of interest, as a definite cause of epiphora could be demonstrated in each of them.

Case reports

Case 1, a 54-year-old female, presented with a history of unilateral epiphora of 7 years' duration. There was no history of injury or of inflammation and the exact date of onset could not be determined. There was, however, a long history of chronic irritation for which drops of various kinds had been instilled over a period of many years. She had been seen previously when, after lacrimal syringing, she was advised that there was no lacrimal pathology; drops were prescribed.

On examination the lacrimal system appeared to be normal; this was confirmed by dacryocystography. Slit-lamp examination, however, revealed the cause of the epiphora. A granuloma, attached by a pedicle to the posterior surface of the lower lid, was occluding the punctum, like a cork in a bottle (Fig. 1). This granuloma was supplied by a blood vessel traversing its pedicle and when withdrawn from the punctum was found to have a conical shape as a result of moulding within the punctum. When in position, it caused epiphora by occluding the punctum, but it could be displaced quite easily by a lacrimal cannula, which entered the canaliculus without difficulty.

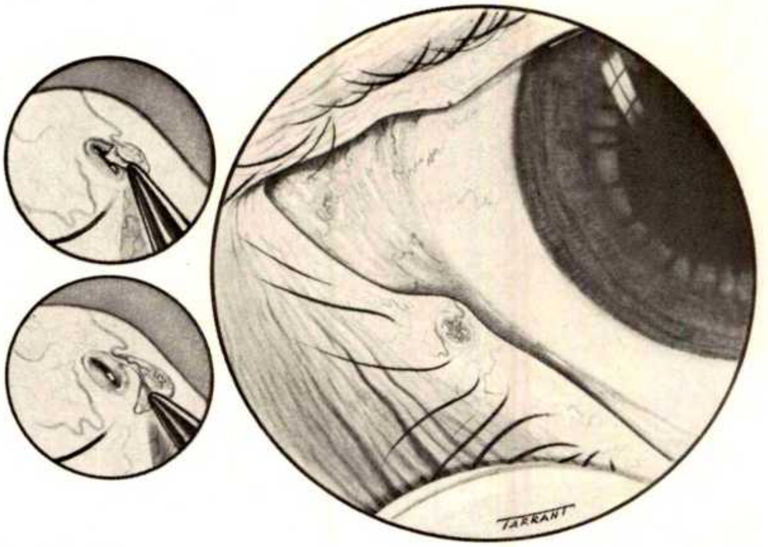

FIG. 1 *Case 1. Granuloma moulded to shape of lacrimal punctum, simulating occlusion*

COMMENT

Once noticed, the cause of obstruction was quite obvious even to the naked eye, especially when the puncta on each side were compared. A normal punctum should always look patent, and on slit-lamp examination its whole depth can be seen. When it does not look

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patent suspicion should be aroused. Occlusions of this kind may follow prolonged use of certain drops (*e.g.* I.D.U.), disuse (*e.g.* in ectropion), and burns from heat, chemicals, or ionizing radiation.

Case 2, a 67-year-old female, complained of bilateral epiphora of "many years" duration. She was most reluctant to submit to lacrimal investigation as she recalled her previous painful experiences. She had attended out-patients departments on several occasions and "got no relief from the drops and a lot of pain from the needle".

Examination revealed gross bilateral conjunctivitis, with very obvious epiphora, excoriation of the skin of lower lids, and commencing bilateral ectropion. Inspection of the puncta suggested an abnormal appearance and a slit-lamp examination was carried out. Each punctum showed a tiny wisp of "cotton-wool like" material extruding from it. Gentle manipulation showed that a complete cast of each canaliculus could be withdrawn from both sides and from both lids (Fig. 2). Each cast demonstrated the irregular lumen of the canaliculus.

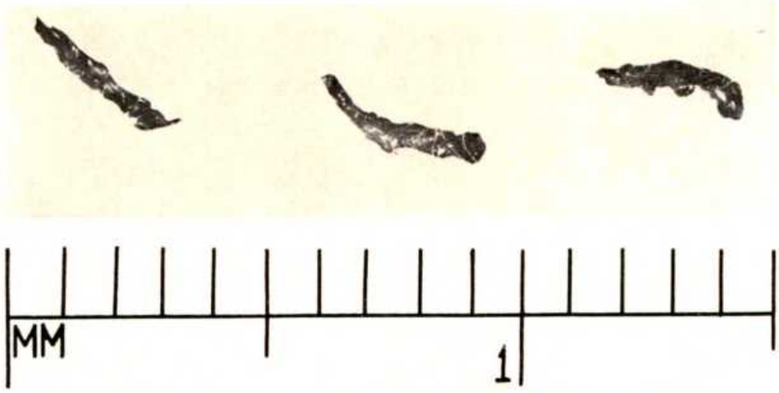


FIG. 2 *Case 2. Canalicular casts. Irregular outlines confirm similar shape of canalicular lumen*

Microscopical examination of one of the casts failed to disclose any pathological organisms. Histopathologically, the cast was composed of fragments of degenerating cells and an amorphous material. Suspected fungi were not demonstrated.

COMMENT

This case illustrates the need for a 'closer look' at the puncta if the immediate naked eye appearance is in the least suspicious.

Sometimes the punctum will be 'obstructed' by an eyelash and the patient will present with a red watery eye (Fig. 3). The redness is always localized to the area of contact between the globe and the protruding eyelash, and ulceration may occur at the site if it has been present for any length of time. The signs and symptoms are much worse if the

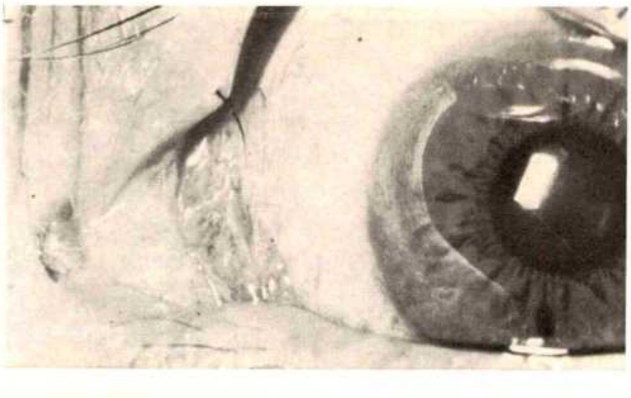


FIG. 3 *Eyelash impacted in upper lacrimal punctum*

impacted 'hair' is not an eyelash but a fragment of hair, such as one sees following a haircut. The epiphora is secondary, *i.e.* not due to the obstruction of the punctum but to the irritation from constant rubbing.

Cure is dramatic.

Case 3, a 57-year-old female, was referred because of a 5-year history of persistent bilateral epiphora. Her history went back to a time when she noticed a change in her facial appearance and a diagnosis of leontiasis ossea was made (Fig. 4). She was treated at first with drops and later with bilateral 3-snip operations; neither of which relieved her symptoms.

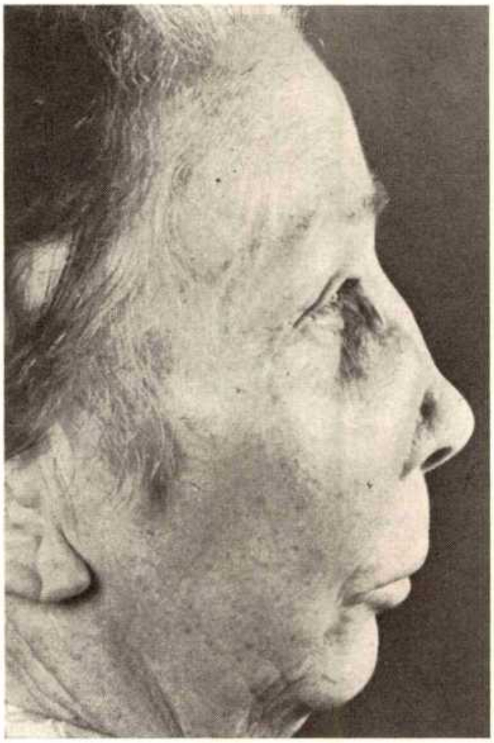
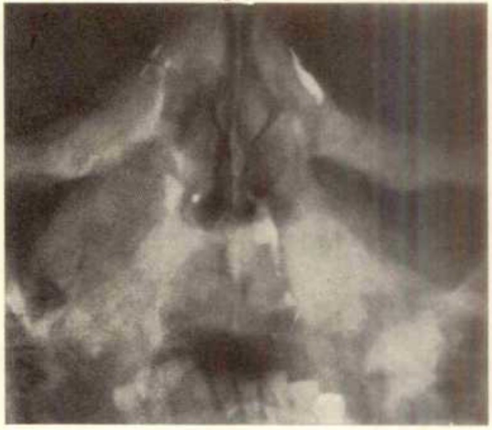


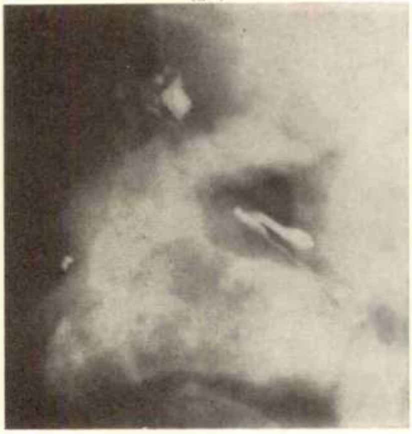
FIG. 4 *Case* 3. *Leontiasis ossea* (*lateral view*)

(5a)



(*a*) *antero-posterior view*

(5b)



(*b*) *lateral view*

FIG. 5 *Case* 3. *Dacryocystogram, showing extensive bony overgrowth with displacement and narrowing of lacrimal canal*

On examination, bilateral 3-snips were noted, and on syringing each sac was entered easily; patency was demonstrated with some pressure. The true state of affairs and the cause of her epiphora were demonstrated by dacryocystography (Fig. 5*a* and *b*).

COMMENT

This case demonstrates how syringing can mislead by giving inadequate information, leading to inaccurate diagnosis and unsuccessful treatment. While it is true that this patient's tear passages were patent on syringing, this finding was only elicited by increasing pressure on the syringe, which helped to overcome the resistance of narrow nasolacrimal ducts. Normal patency was mistakenly inferred.

In investigating a case of epiphora the following points are considered important. The anatomical arrangement along the whole of the lacrimal apparatus must be borne in mind. Any obstructions encountered should not be overcome forcibly at the time of the investigation. This will only result in discomfort to the patient and a little bleeding, followed by further fibrosis. Both canaliculi must be investigated, as it is commonly found that the upper is patent, whereas the lower may be blocked.

The passage of fluid into the nose during syringing conveys little positive information. If it is remembered that flow equals pressure over resistance ($F = \frac{P}{R}$), then it becomes obvious that the pressure exerted by the thumb on the plunger of the syringe will overcome the resistance of a partial obstruction, showing apparent patency. It is true that experience will indicate how much pressure is required to achieve flow, but the most adequate diagnostic information can be obtained only by dacryocystography. The dacryocystogram is an essential part of the investigation of epiphora. It not only localizes the site of obstruction but gives additional information – for example, the presence of loculi, foreign bodies, etc. Briefly, the method consists of injecting Neohydriol into the sac through the upper or lower canaliculus, depending on which is patent. There is no pre-determined quantity of fluid that needs to be injected. The quantity is determined by the volume of the sac. If partial patency exists, the patient is asked to say when the fluid is tasted. If obstruction is complete the fluid will regurgitate immediately through one or other of the puncta. If the medium regurgitates immediately through the opposite punctum the *x* ray may be somewhat deceptive as only a small quantity will have entered the sac. This need not necessarily mean that the sac is obstructed. Experience has shown that this usually means that the common opening is isolated by adhesion of the mucosal folds guarding the common opening in the valve of Rosenmuller. It may be true that the sac is completely obliterated, but one's suspicions should be aroused as to other possibilities and special attention should then be directed to the common opening at the time of surgery. Failure to appreciate this point will result in failure to achieve success. One further point should be considered. If, when the opaque medium is injected, none is regurgitated or tasted by the patient, one should suspect one of two possibilities; either a false passage may have been created forcing the fluid into the surrounding tissues with discomfort to the patient (this is of little consequence and is eventually absorbed) or, in cases of middle third fracture of the face, the lower end of the nasolacrimal duct is displaced. The upper end may then empty into the maxillary sinus and the opaque medium in such a case may fill the maxillary sinus so that the usual symptoms of a full sac are not forthcoming.

In this case the puncta may well have been reduced in size but a 3-snip operation should never be performed without first establishing that the rest of the lacrimal apparatus is normal. This could only have been shown by dacryocystography.

Case 4, a 60-year-old male, presented with unilateral epiphora of sudden onset. There was no relevant previous history other than one of recurring nasal polypi, which had been treated surgically. On closer questioning he thought that his epiphora had started after the most recent operation on his nose, and it was established that this was an inferior turbinectomy.

On investigation he was found to have normal puncta, canaliculi, and sac, but there was a complete obstruction at the lower end of the nasolacrimal duct. This was established by dacryocystography (Fig. 6, opposite).

COMMENT

This was a case of obstruction of the end of the nasolacrimal duct by fibrosis following turbinectomy, and illustrates the need to pursue a history, so that where possible, logical cause-and-effect relationships can be established. Occasionally, patients forget previous incidents, especially if in understandable ignorance they think that there is no link between the symptom and the underlying pathology. On several occasions the author has been surprised to find Summerskill tubes embedded in the lacrimal area during the course of a dacryocystorhinostomy, the patient having forgotten completely that he has had previous surgery.

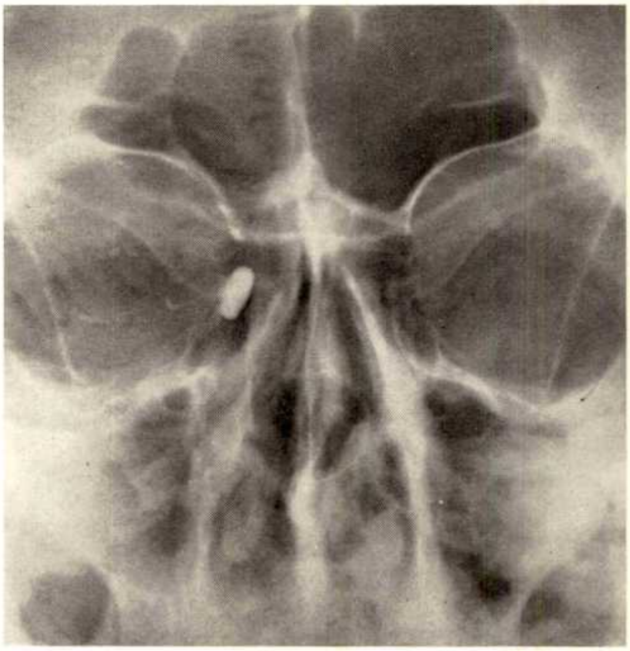


FIG. 6 *Case 4. Total obstruction of lacrimal duct*

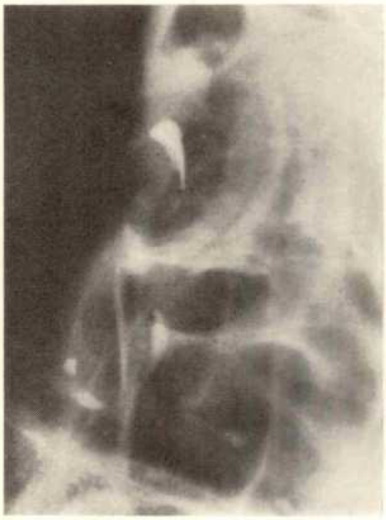


FIG. 7 *Case 5. Lateral view of dacryocystogram, showing filling defect suggestive of a dacryolith which was confirmed at operation*

Case 5, an otherwise healthy 38-year-old female, presented with a year's history of unilateral epiphora. During the course of detailed questioning no attributable cause of obstruction was revealed; a chance remark about occasional epistaxis went unnoticed.

On lacrimal syringing, partial patency was achieved after applying a little pressure on the plunger of the syringe. Dacryocystography showed partial obstruction of the nasolacrimal duct with a filling defect in the sac suggesting the presence of a dacryolith (Fig. 7).

Surgery confirmed the presence of a dacryolith surrounded by much soft granulomatous tissue. The sac wall itself was spongy, with a tendency to bleed and a grossly undulating mucosal surface. The pathology report read as follows:

"*Micro:* (**1**) Sections of the 'granuloma' show hyperplastic lymphoid tissue in the wall of the lacrimal sac. The sac lining consists of a single layer of columnar epithelium. In places this appears to be partly destroyed by a chronic inflammatory infiltrate. No specific infective agent is apparent either in haematoxylin and eosin sections or in special stains.

(**2**) The 'lacrimal sac' appears to me to have the structure of an angioma rather than a lacrimal sac. There are several vascular spaces, one quite large, apparently communicating, in a connective tissue stroma diffusely infiltrated with chronic inflammatory cells.

Diagnosis: (1) Reactive lymphoid tissue in wall of lacrimal duct (or sac).

(2) Para lacrimal duct (sac) angioma."

COMMENT

It is tempting to postulate that this patient's epiphora was caused by an angiomatous malformation. This would explain the epistaxis and the slow development of lacrimal stasis, leading to dacryolith formation. In turn this would give rise to an inflammatory reaction which then precipitated the symptoms. Dacryocystorhinostomy relieved the patient of her symptoms.

Cases 6 and 7 Both these patients were young married women (one a qualified nurse) who claimed that epiphora commenced after taking oral contraceptives. When these were withdrawn the epiphora ceased.

COMMENT

The association of epiphora with 'The Pill' should be kept in mind when young women complain of watering eyes without apparent cause. A few unnecessary dacryocystorhinostomies may be avoided by withdrawing the pill to see if the symptoms disappear. As yet, there is no positive proof of this association or the mechanism by which epiphora is produced.

It is a pleasure to express my gratitude to the staff of the Department of Medical Photography, Queen Victoria Hospital, East Grinstead, for the excellence of the photographs.

Brit. J. Ophthal. (1971) **55**, 565

Tuberculoma of the orbit and lacrimal gland

ALY MORTADA
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The three following cases of tuberculoma, one of the orbit and two of the lacrimal gland, are described because of their rarity (Offret, 1939; Duke-Elder, 1952).

Case reports

The three patients reported below were in good general condition, with no enlargement of the lymph glands, liver, or spleen. Apart from increased lymphocytes the blood count was normal. The urine was free from albumin and sugar. The blood pressure, pulse rate, and body temperature were normal. The faeces showed no parasitic ova. There was no abnormality of the chest, air passages, abdomen, skin, or bones. The blood Wassermann reaction was negative. There were no septic foci in the body. Skull *x* rays showed no abnormality of the orbital bones. There was no history of trauma, and no signs of syphilis, sarcoidosis, or Mikulicz's disease. The tuberculin test was positive.

Case 1, an obese woman aged 35 years, complained of gradual painless proptosis of the left eye of 6 months' duration.

The right eye and fundus were normal, and the visual acuity was 6/6.

The left eye showed a forward proptosis of 20 mm. (Hertel) with downwards limitation of ocular movements. The fundus was normal and the visual acuity was 6/9. A hard orbital mass was felt in the lower eyelid extending backwards below the eye into the orbit. When the mass was pressed backwards the globe was made to protrude forwards.

The tumour, which was removed through a lower fornix conjunctival incision, measured 2·5 × 1·5 × 1 cm. and was pink, firm, and encapsulated. Histopathological examination showed a granulomatous structure with giant cells (Fig. 1) which is characteristic of tuberculoma, but tubercular organisms were not seen.

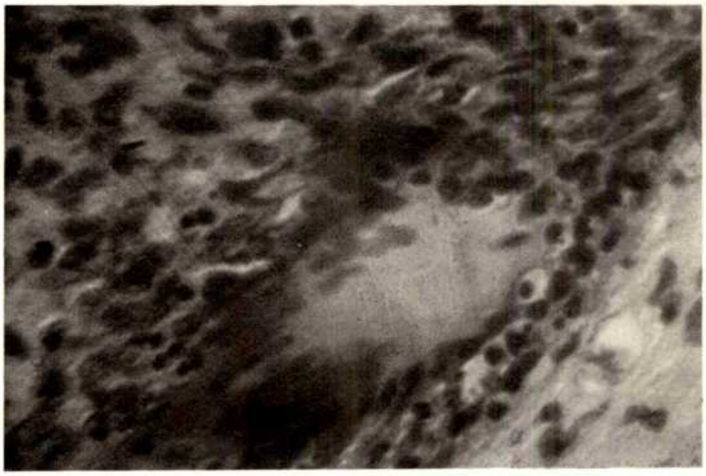

FIG. 1 *Case 1. Tuberculoma of orbit, section showing giant cell system.* ×540

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Case 2, a woman aged 40 years, complained of gradual painless proptosis of the right eye of 7 months' duration (Fig. 2).

The left eye was normal.

The right upper eyelid showed ptosis, the eye was pushed downwards and inwards with limitation of ocular movements up and out. The fundus was normal and the visual acuity 6/12. The proptosis measured 21 mm. (Hertel), there was oedema of the right upper lid, and the palpebral and orbital parts of the right lacrimal gland were palpable. Both parts of the gland were excised.

Histopathological examination of the mass showed a tuberculoma of the lacrimal gland with typical giant cell systems (Fig. 3).

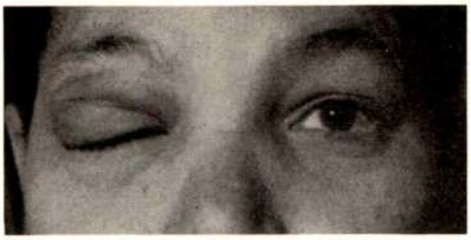

FIG. 2 *Case 2. Right proptosis and ptosis due to tuberculoma of lacrimal gland of 7 months' duration in a woman aged 40 years*

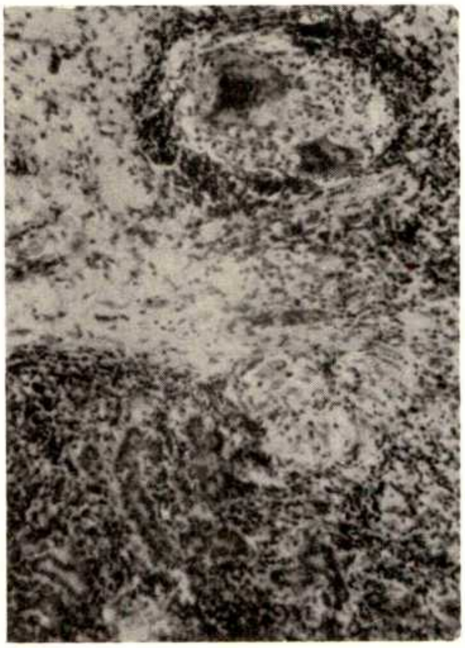

FIG. 3 *Case 2. Tuberculoma of lacrimal gland, section showing giant cell system among acini of gland.* × 120

Case 3, a woman aged 38 years, complained of gradual right proptosis of 5 months' duration (Fig. 4).

The left eye was normal with a visual acuity of 6/9.

There was right ptosis, oedema of the right eyelids, and chemosis of the conjunctiva, with proptosis downwards measuring 21 mm. (Hertel). There was limitation of ocular movements upwards. The right fundus showed engorged retinal vessels and a visual acuity of 6/18. The palpebral and orbital parts of the right lacrimal gland were enlarged and were excised.

Histopathological examination showed a tuberculoma of the lacrimal gland with typical giant cell systems (Fig. 5). Sections were negative for tubercular organisms.

In these three patients, the excision of the orbital mass was followed by a course of intramuscular streptomycin injections. There was no recurrence of the orbital mass or proptosis during a 5-year follow-up.

Discussion

Tuberculosis of the lacrimal gland was first described by Abadie (1881) and since then many reports have appeared in the literature (Motto and Rowen, 1929; Wilson, 1937; Heath, 1947). The infection is usually haematogenous and the acute miliary form is rare. The localized isolated form seen in these three cases is more important clinically, and often occurs in persons with healed lesion of the lungs, lymph glands, or bones. The isolated form is usually of the sclerotic and rarely of the caseous type.

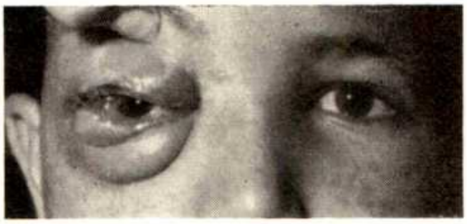

FIG. 4 *Case 3. Right proptosis, ptosis, and oedema of lids due to tuberculoma of lacrimal gland of 5 months' duration in a woman aged 38 years*

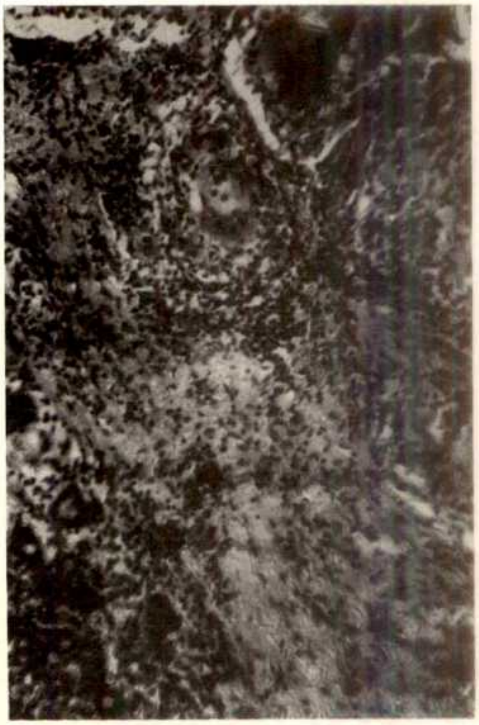

FIG. 5 *Case 3. Tuberculoma of lacrimal gland, showing giant cell system among acini of gland.* × 120

Cases of orbital tuberculoma may present as unilateral proptosis, as a unilateral partial or complete superior orbital fissure syndrome, or as an orbital apex syndrome of uncertain origin (Mortada, 1961). The diagnosis can be confirmed only by orbital exploration, biopsy, and histopathological examination.

Tuberculoma of the orbit and lacrimal gland usually affects females of 35 to 50 years of age as in these three cases. Excision of the lesion followed by streptomycin injections gives complete cure with no recurrence of the proptosis or the orbital mass.

Summary

(1) Three rare cases of tuberculoma, one of the orbit and two of the lacrimal gland, are described.

(2) The three cases occurred in women aged 35, 38, and 40 years.

(3) Diagnosis was by excision of the tumour and histopathological examination.

(4) Apart from a positive Mantoux test, there were no active tuberculous lesions in the lungs, lymph glands, bones, or skin. There may have been a healed focus in the lungs.

(5) A 5-year follow-up did not show any recurrence of the orbital mass or the proptosis.

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Brit. J. Ophthal. (1971) **55,** 568

Congenital facial diplegia

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Congenital facial paralysis may occur alone or in association with other anomalies (Duke-Elder, 1964). The most common association is with the ocular motor nerves, particularly the VIth (Moebius syndrome).

Henderson (1939) reviewed 61 cases, showing a high incidence of motor palsies and other defects.

Case report

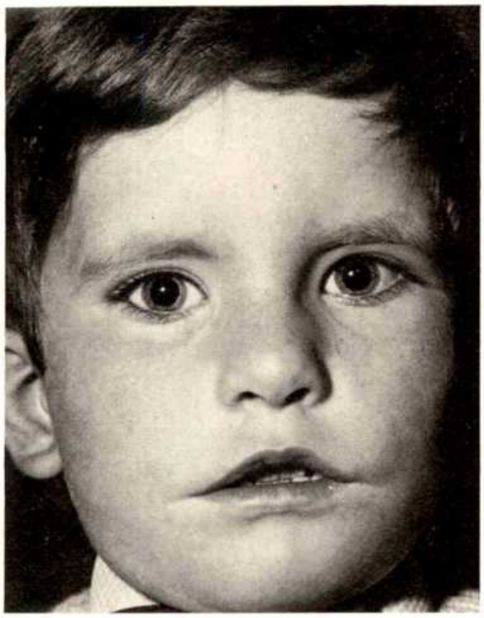
This patient, a boy aged 4 years, was referred to the Paediatric Department by his general practitioner who had noticed his stiff upper lip, and that he was unable to smile or wrinkle his face. In infancy he had had difficulty in sucking a bottle, but could feed from the breast. He was later able to swallow using a cup, without dribbling, but could not suck from a straw. He had had recurrent ocular infections until he was 2 or 3 years old.

FAMILY HISTORY

There was no family history of muscular or neurological disease, and no consanguinity. There were no complications during pregnancy and the confinement was normal.

EXAMINATION

The patient had an expressionless face with no movement of the facial muscles (Buster Keaton facies) (Fig. 1). He was unable to close his eyes fully, smile, frown, raise his eyebrows, or purse his lips to whistle. Bell's phenomenon was observed on attempted closure of the eyes (Fig. 2). The mouth



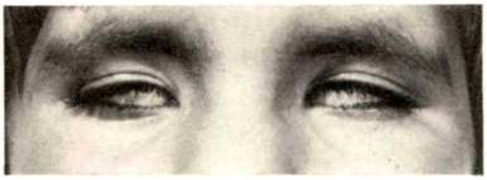


FIG. 2 *Open eyelids on attempting to close the eyes*

FIG. 1 *General appearance at age 5*

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was always slightly open and the upper lip prominent. The only movement of the mouth was that due to opening the jaw and to contraction of platysma in the neck. He had no difficulty in swallowing. The tongue was normal in size and could be protruded normally with no sign of twitching. The remainder of the examination gave normal results. Ocular movements were full. There was no nystagmus. Convergence was normal. There was watering of both eyes, but no discharge. Hearing was normal. The tear ducts were syringed and found to be patent.

TREATMENT

The symptoms were relieved by prescribing glasses with side-pieces to prevent dust or dirt from entering the eyes.

Summary

A case of congenital facial diplegia is described in which there was no involvement of the ocular muscles and no systemic defects.

We wish to thank the Department of Medical Illustration at the Royal Gwent Hospital for providing the illustrations.

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Brit. J. Ophthal. (1971) **55**, 570

Oculo-mandibular synkinesis

PREM SINGH AND BIJOYANANDA PATNAIK

From the Department of Ophthalmology, Maulana Azad Medical College, and the Associated Irwin and G. B. Pant Hospitals, New Delhi, India

Synkinetic movement of the mandible with ocular movement is a rare anomaly. Carmichael and Critchley (1925) noticed that, when the eyes were rapidly turned horizontally first to one side and then to the other, there was protrusion of the mandible with deviation to the contralateral side. The movement may be associated with depression of the contralateral and raising of the ipsilateral eyebrow. Walsh (1957) mentioned one case in which, besides these features, there was a concomitant contraction of the muscles of the ipsilateral side of the mouth.

The jaw movement is often too slight and subtle to be satisfactorily documented by static photography, and we have therefore devised a method whereby oculo-fronto-mandibular synkinesis may be measured using the Vernier displacement principle to record the small lateral movement of the jaw.

Material and method

An experiment was carried out with a 19-year-old youth with anisometropic amblyopia of the left eye. An out-patient record card with parallel vertical lines was held in position in front of the throat, just over the larynx, by a thread round the neck. Jaw movements did not produce any movement of this card.

A small piece from a similar card with similar lines was then fixed over the chin with sticking plaster. Photographs were taken in the primary position (Fig. 1) and while the patient looked to the left with and without the guide cards (Figs 2 and 3). The patient's head and the camera remained fixed.

Result

When the patient looked to the left, the jaw showed a definite small movement to the ipsilateral side (contralateral in previously reported cases). This is difficult to see in Fig. 2 but is easily measured in Fig. 3. He also showed a raising of the ipsilateral eyebrow with wrinkling of the forehead. The contralateral eyebrow did not show any depression.

Summary

A simple method has been devised for recording small movements of the jaw in a case of oculo-mandibular synkinesis.

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Address for reprints: Dr. P. Singh, Department of Ophthalmology, Maulana Azad Medical College, and the Associated Irwin and G. B. Pant Hospitals, New Delhi, India

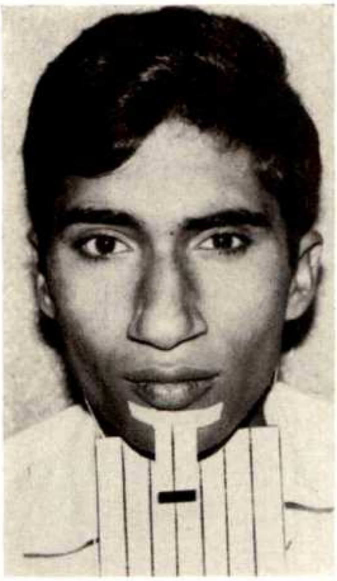

FIG. 1 *Primary position*

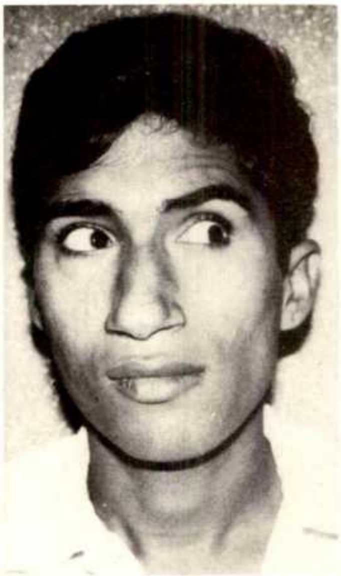

FIG. 2 *Patient looking to the left; the jaw movement is difficult to perceive without the indicator*

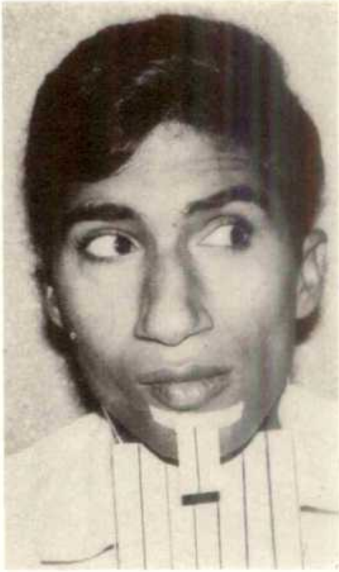

FIG. 3 *Patient looking to the left, showing the Vernier shift caused by the jaw movement*

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Brit. J. Ophthal. (1971) **55**, 572

Ophthalmoscope densitometer

J. MARSHALL AND D. A. PALMER

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Current research on laser thresholds for retinal injury have shown that, for a given set of laser parameters, the extent of retinal damage is dependent on the degree of fundus pigmentation (Kohtiao, Resnick, Newton, and Schwell, 1966; Vassiliadis, Rosan, Peabody, Zweng, and Honey, 1966; Marshall, 1970). The pigmentation arises from three components, blood, visual pigments, and melanin, and varies in intensity both between individuals and within a single eye. The greater part of fundus pigmentation is due to the melanin granules in the retinal pigment epithelium, and most types of laser damage result from the dissipation of energy absorbed by this layer (Fine and Geeraets, 1965; King and Geeraets, 1968; Marshall and Mellerio, 1970).

We have designed an instrument to measure the pigmentation in the fundus and thus to indicate the susceptibility to laser coagulation. It should be noted, however, that in short wavelength laser exposures such as Argon or Krypton the density of visual pigments appears more important than total fundus pigmentation (Rosan, Rose, Zweng, Flocks, Peabody, and Vassiliades, 1967; Rosan, Flocks, Vassiliades, Rose, Peabody, and Hammond, 1969; L'Esperance, 1969; Bresnick, Frisch, Powell, Landers, Holst, and Dallas, 1970) and in these cases complex and expensive reflectometers are required (Weale, 1959, 1965; Rushton, 1965).

Our system can be fitted as an extension tube to almost all currently available ophthalmoscopes and laser ophthalmoscopes. A ray diagram is shown in the Figure. The conventional ophthalmoscope is represented by the lenses F_1, F_2 and the mirror M_1. In our modification, light from the subject's fundus passing through the aperture in the mirror M_1, is focused by F_3 at the field lens F_4. This image is viewed through F_5. The mirror M_2 is positioned so that a calibration beam (dotted) can be introduced for comparison with the fundus image. The calibration beam passes through a wheel of neutral density filter at W. The observer views a split field half of which is the subject's fundus AB, and the other half the calibration field BC.

The pigment density of the subject's fundus is measured by revolving the filter wheel W until a density is obtained for a match with the subject's fundus. The densities of the filters in the wheel must be known and can be selected to suit the species to be examined. To distinguish the amount of pigmentation due to melanin in the pigment epithelium from the fundus pigmentation due either to visual pigments or to haemoglobin, a match is obtained for an albino eye or for the optic nerve head in a pigmented eye. This value represents the zero pigmentation condition and should be subtracted from the values obtained from pigmented retinal areas. Matches are more easily achieved in monochromatic light and suitable filters can be introduced into both beams at the various laser wavelengths.

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Address for reprints: J. Marshall Esq., Department of Anatomy, Institute of Ophthalmology, Judd St., London, WC1H 9QS

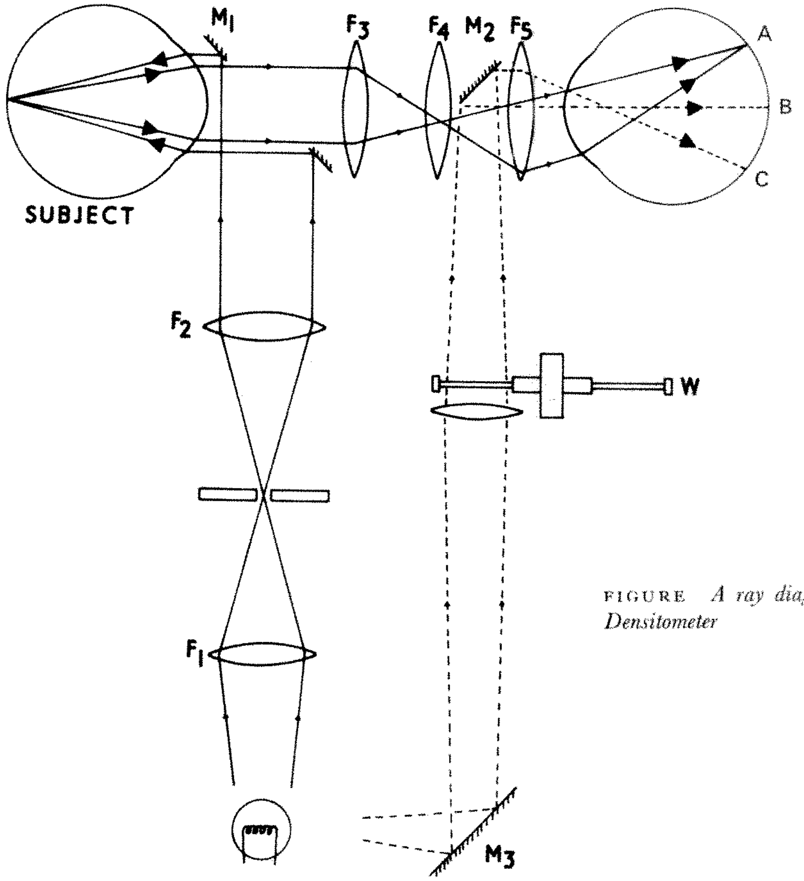

FIGURE *A ray diagram of the Fundus Densitometer*

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Book reviews

A System of Ophthalmology. Vol. 12 Neuro-ophthalmology. By S. Duke-Elder and G. I. Scott. 1971. Pp. 994, 830 figs, 12 col. pl., bibl. Kimpton, London. (£13.00).

It is generally recognized how impossible it is to investigate a process without interfering with its mechanism and studying the result under controlled conditions. In a sense, neuro-ophthalmology is an account of experimental models set up by pathological lesions and our understanding of the physiology of the nervous system owes much to careful clinical observation of the results of such lesions collated with pathological findings. Herein lies the fascination of Volume XII of the *System of Ophthalmology*. The subject ranges widely and presents a profound challenge to the pen of Sir Stewart in width and depth, but when the reader has reached page 970, it must be admitted that the challenge has been met and subdued. All aspects appear to fall inevitably into place.

Section I on the Visual System traces the sensory pathway from the optic nerve to the occipital cortex and ends with a chapter on the higher visual system, which includes discussion on cortical blindness, the agnosias and aphasias, hallucinations, and psychogenic disorders.

Section II covers the pupillary and ciliary systems and Section III the motor system, including nystagmus and lid movements. Section IV copes with the trigeminal nerve and the secretory disturbances of the lacrimal apparatus.

No attempt is made to describe in detail the techniques or findings of radiography, radiotomography, pneumoencephalography, arteriography, phlebography, electroencephalography, or the use of radioactive isotopes. Nor indeed is there any need to delve into the purlieus of our sister specialty, for neuro-ophthalmology has a feast of its own to offer served in splendid style by the two authors of Volume XII.

Methods of Ophthalmological Investigation (Die ophthalmologischen Untersuchungsmethoden). Vol. 1. Edited by W. Straub. 1970. Pp. 546, 542 figs, refs. Enke, Stuttgart. (DM 128).

This book forms the first of two volumes on this subject. Methods of examination in ophthalmology are becoming so complex and specialized that the publication of this book is very welcome especially as the many authors are experts in their own fields. The general plan is to give a short relevant historical introduction to the methods of examination with emphasis on the underlying principles used, the technical methods, and their application.

The book has an ambitious scope. Draeger and Richert describe the external examination of the eye. Müller gives a long chapter on microbiology. Tear secretion and tear drainage deserve rather a larger section, but Goldmann, as usual, has written a long and excellent section on focal illumination. Examination of the pupil is described by Schrader and ophthalmoscopy by Sautter and Rassow. Other sections are devoted to spectral reflectometry, tonometry and tonography, ophthalmodynamometry, radiological diagnosis, ultrasound, and the use of radioactive isotopes.

This book can be highly recommended and one looks forward to the second volume, but frequent revision will be required in order to keep it up to date.

Perspectives in Ophthalmology. Edited by H. E. Henkes. 1968. Pp. 268, figures, bibl. Excerpta Medica Monograph, Amsterdam. (£6.70).

This volume, which contains material presented at a postgraduate teaching course at the Rotterdam Hospital in 1967, is in three sections. The first discusses the angiopathies of the retina and choroid and gives a great deal of interesting information on how they may be investigated. The second deals with ophthalmic plastic surgery and in particular with surgery of the lacrimal apparatus and with the implantation of intra-ocular acrylic lenses, and the third with visuo-medical aspects of road traffic safety. This is a useful book which should be read by all ophthalmic surgeons.

Cryo-ophthalmology (Cryo-ophtalmologie). Report presented to the *Société française d'ophtalmologie* by P. G. MOREAU and J. HAUT. 1971. Pp. 746, 278 figs, refs. Masson, Paris.

This book, which is the latest of the excellent annual publications of the French Ophthalmological Society, gives a comprehensive description of freezing techniques in ophthalmology, including detailed accounts of the principles involved, the apparatus, and experimental work on the effects of freezing on various ocular tissues.

The clinical applications of cryotherapy are discussed in detail, both the established and the more controversial aspects being documented assiduously. A chapter on the conservation of ocular tissues by freezing concludes the volume.

This book offers a welcome review of this modern subject which has such a wide application. It is too early to assess which of its uses will find a permanent place in ophthalmological practice, but there is no doubt that many are already accepted as an integral part of our day-to-day operative work.

Ophthalmic Cryotherapy (Die Kryotherapie in der Ophthalmologie). By D. FORLANI, G. TIBERIO, and N. NEGRONI, translated by H. RÖSSLER. 1970. Pp. 83. *Klin. Mbl. Augenheilk.*, Suppl. 55. Enke, Stuttgart. (DM 14).

This booklet, first published in Italian in 1968, gives comprehensive information on most aspects of ophthalmic cryotherapy. Its clear and precise style reveals the expert teacher. A short historical survey and a very short chapter about the histological changes due to cryoapplication are followed by a detailed description of the available cryoapplicators. The main sections are naturally dedicated to cryoextraction of cataract and to cryopexy in retinal detachment. The authors believe that cryoextraction is the safest method of intracapsular cataract removal, but the procedure has to be properly executed with a modern lightweight instrument to prevent avoidable complications, and such instruments are unfortunately very expensive. By this method the lens capsule is not often torn, even in intumescent, hypermature, and complicated cataract interventions, and the danger to the vitreous is also much reduced. The main disadvantages are the maltreatment of the iris and the need for skilled assistance. In favourable cases of retinal detachment and in cases requiring prophylactic measures, cryopexy exposes the eye to much less danger than diathermy. It is even preferable to photo-coagulation as it does not produce retinal haemorrhages.

Cryotherapy has its uses in other conditions, such as chronic glaucoma, virus keratitis, and trachoma. It is a pity that this small book contains no figures, for illustrations make a more forceful impression than the printed word.

Notes

Clear print

Conference, October 20, 1971

The Library Association and the National Association for the Education of the Partially Sighted are to hold a one-day Conference on Clear Print with special reference to the needs of the visually handicapped reader on Wednesday, October 20, 1971, at the Commonwealth Hall, Royal Commonwealth Society, London, W.C.2.

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European Ophthalmic Pathology Society

Annual Meeting, London, April 25–28, 1971

A Joint Meeting of the European Ophthalmic Pathology Society (celebrating its 10th anniversary) and the Verhoeff Society of America (celebrating its 25th anniversary) was held at the School of Pharmacy, London, England, on April 25 to 28, 1971. This was a unique occasion for the members of both societies, and the members of the Verhoeff Society, with their wives, were the guests of the E.O.P.S. for the whole meeting.

Professor Norman Ashton, assisted by members of his staff, organized the scientific and social programmes, the scientific sessions being attended by 29 members of the E.O.P.S. and 25 members of the Verhoeff Society.

At the invitation of the Verhoeff Society, a cocktail party was held on the Sunday evening and this was followed by a buffet supper and a private visit to Westminster Abbey where the members were received and conducted round by the Abbey staff. On Tuesday a Reception was given by the Corporation of London, in the presence of the Lord Mayor, at the Mansion House, and an informal dinner was later greatly enjoyed at "The Anchor", Bankside. The Annual Banquet on the final evening was held in the historic Goldsmiths' Hall in the City of London.

The ladies of the E.O.P.S. entertained the American ladies and together they visited Hampton Court and Windsor, with lunch at Great Fosters, and Harrods for a shopping morning, followed by lunch in the Store; and the next day took a river trip to the Tower of London and Greenwich, where lunch was taken at the Trafalgar Tavern.

The 29 Members of E.O.P.S. attending were:

Prof. J. Casanovas, President (*Spain*)

Dr. S. Ry Andersen (*Denmark*)
Prof. K. Arnesen (*Norway*)
Prof. N. Ashton (*Gt. Britain*)
Dr. R. Barry (*Gt. Britain*)
Prof. P. Bec (*France*)
Dr. B. A. Bembridge (*Gt. Britain*)
Prof. J. Böck (*Austria*)
Dr. A. Brini (*France*)
Prof. J. Cunha-Vaz (*Portugal*)
Dr. C. Cook (*Gt. Britain*)
Prof. P. Danis (*Belgium*)
Dr. P. Dhermy (*France*)
Prof. H. Fanta (*Austria*)
Dr. A. Garner (*Gt. Britain*)
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Dr. Joan Mullaney (*Ireland*)
Dr. G. Naumann (*W. Germany*)
Prof. A. Nover (*W. Germany*)
Prof. R. Seitz (*W. Germany*)
Prof. A. H. A. Tarkkanen (*Finland*)

The 25 Verhoeff Society Members attending were:

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Dr. F. Blodi
Dr. M. Boniuk
Dr. D. Cogan
Dr. V. Curtin
Dr. W. Davies
Dr. A. Ferry
Dr. R. Font
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Dr. A. Reese
Dr. T. Sanders
Dr. T. Smith
Dr. W. Spencer
Dr. J. Wadsworth

The next (11th) meeting of the E.O.P.S. will be held in Helsinki (Finland) on June 8 to 19, 1972 when Prof. A. H. A. Tarkkanen will act as organizing secretary.

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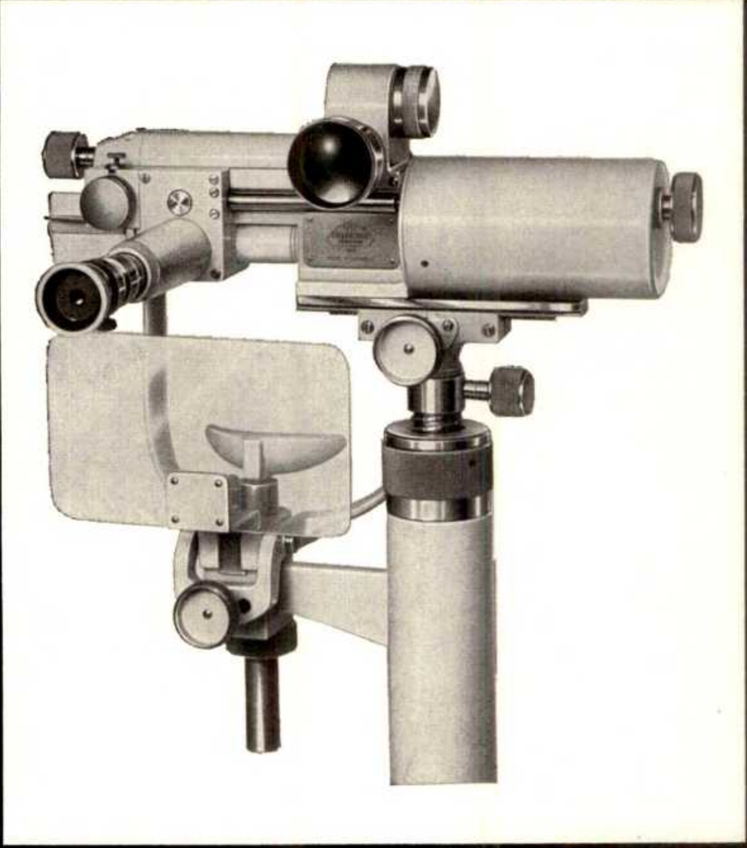

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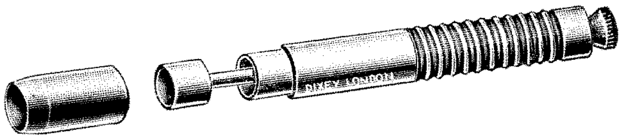

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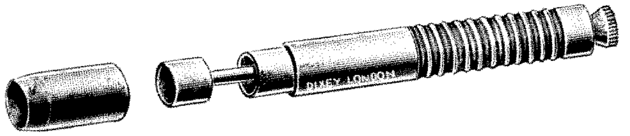

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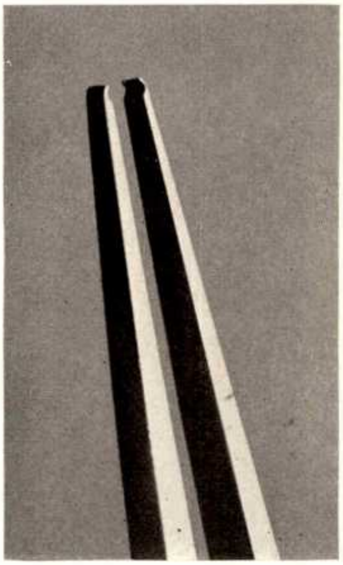

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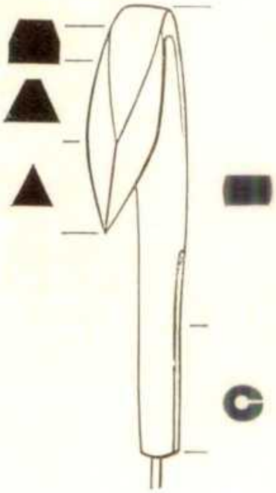

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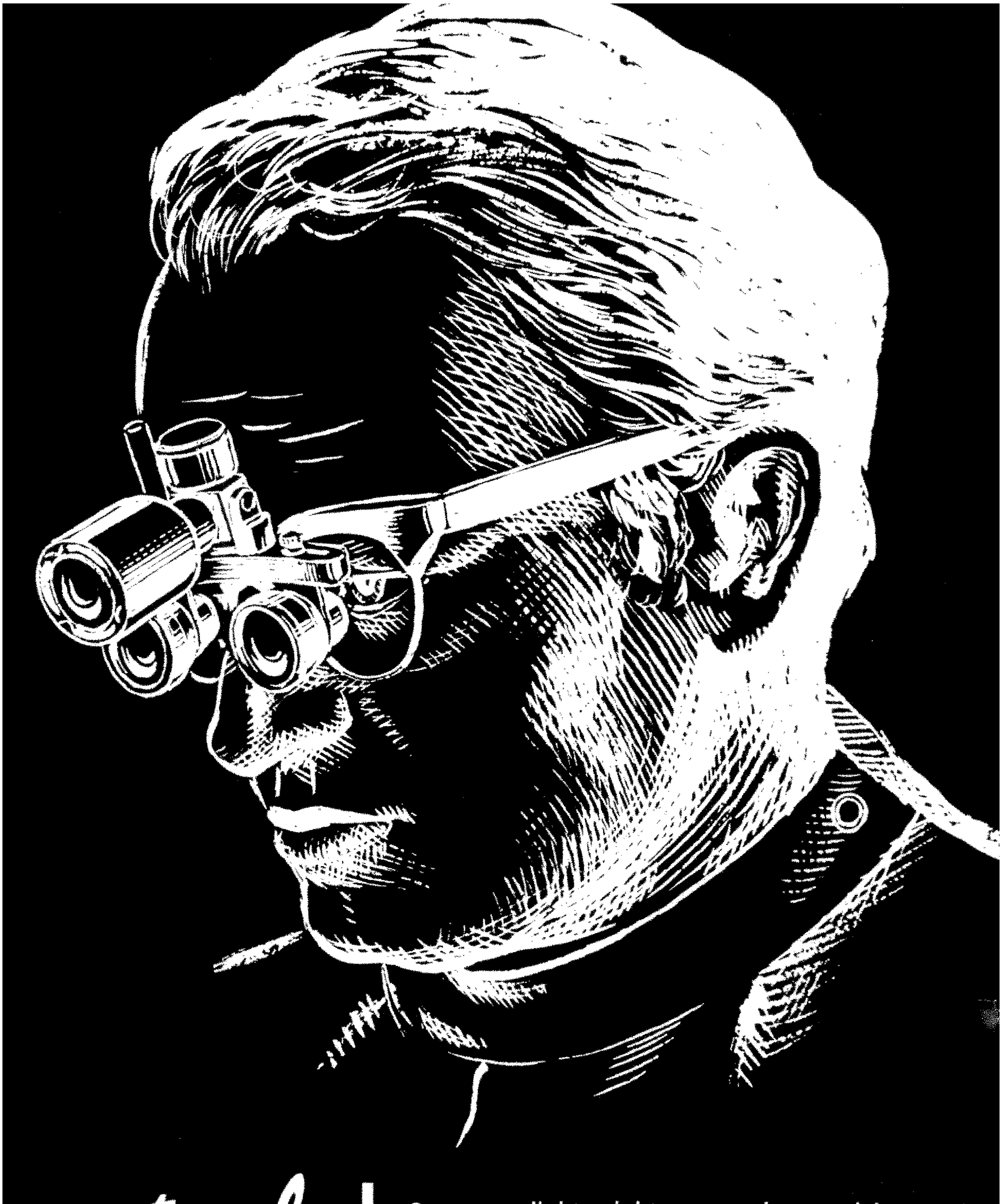

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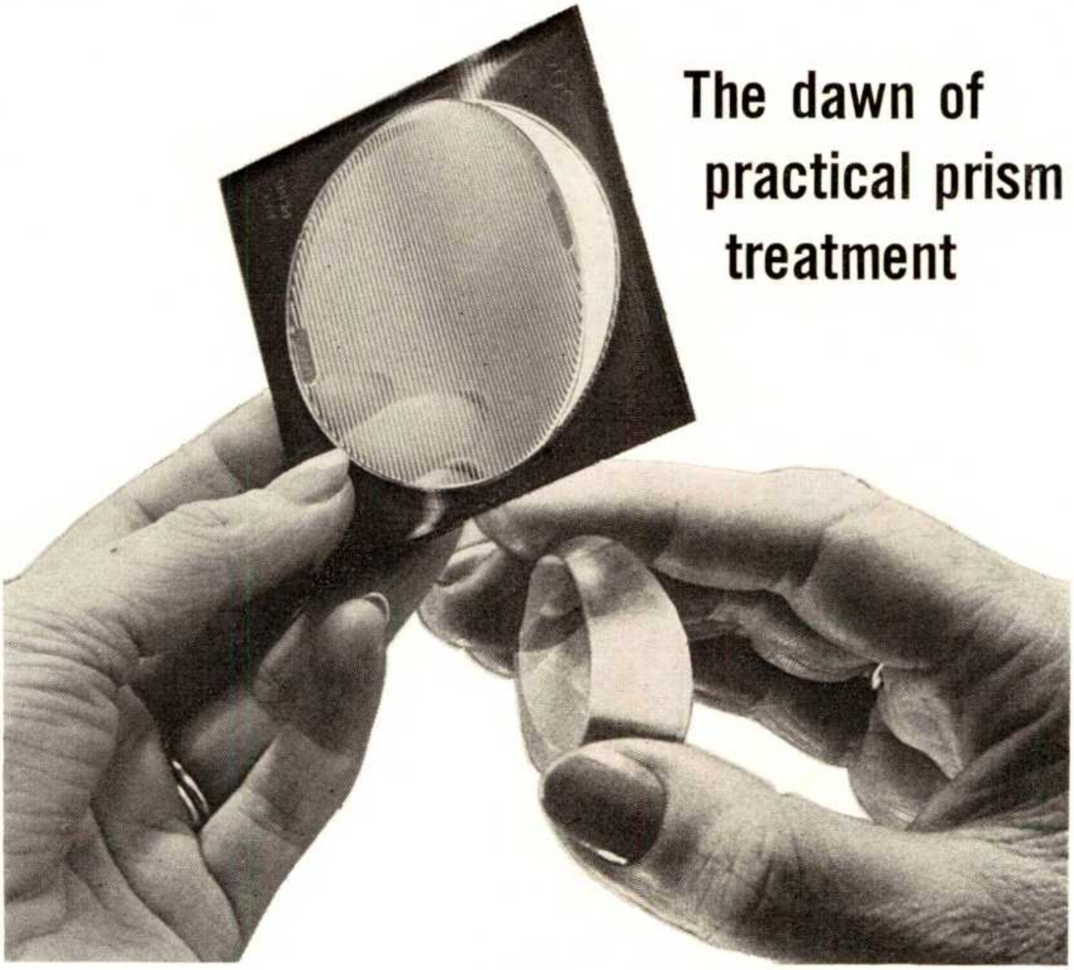

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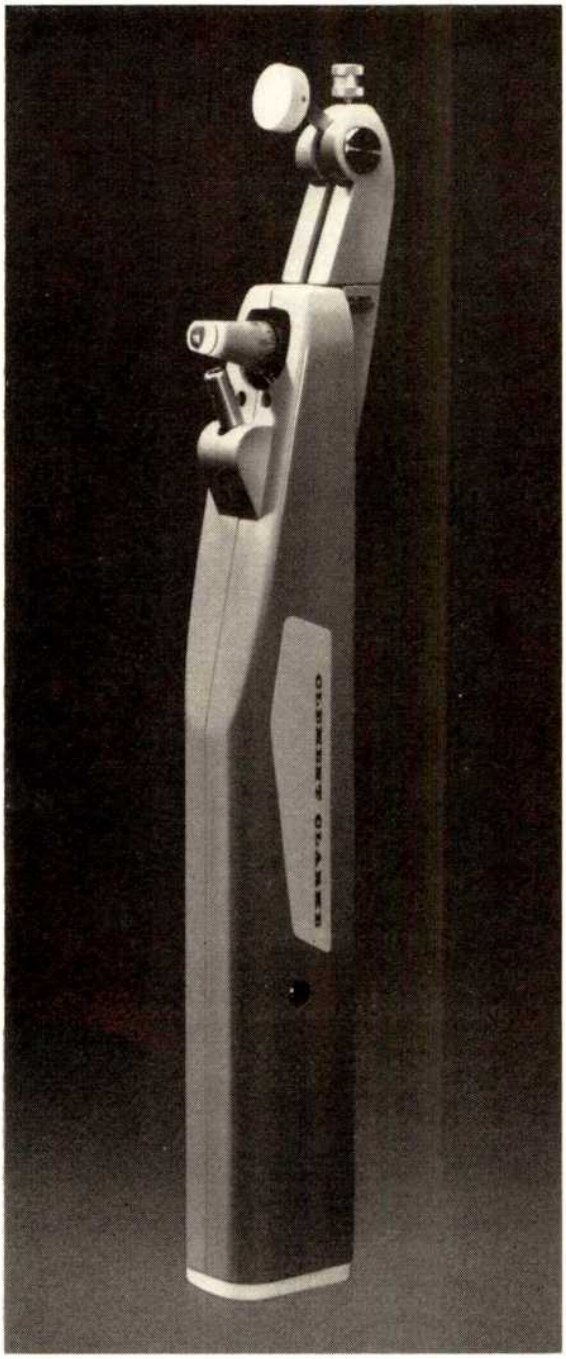

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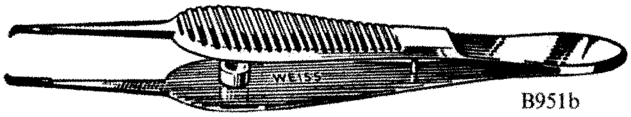

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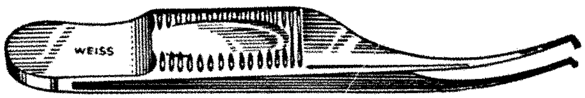

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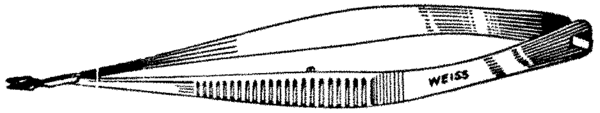

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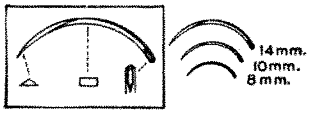

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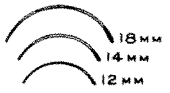

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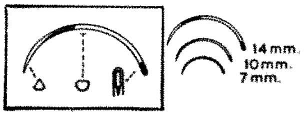

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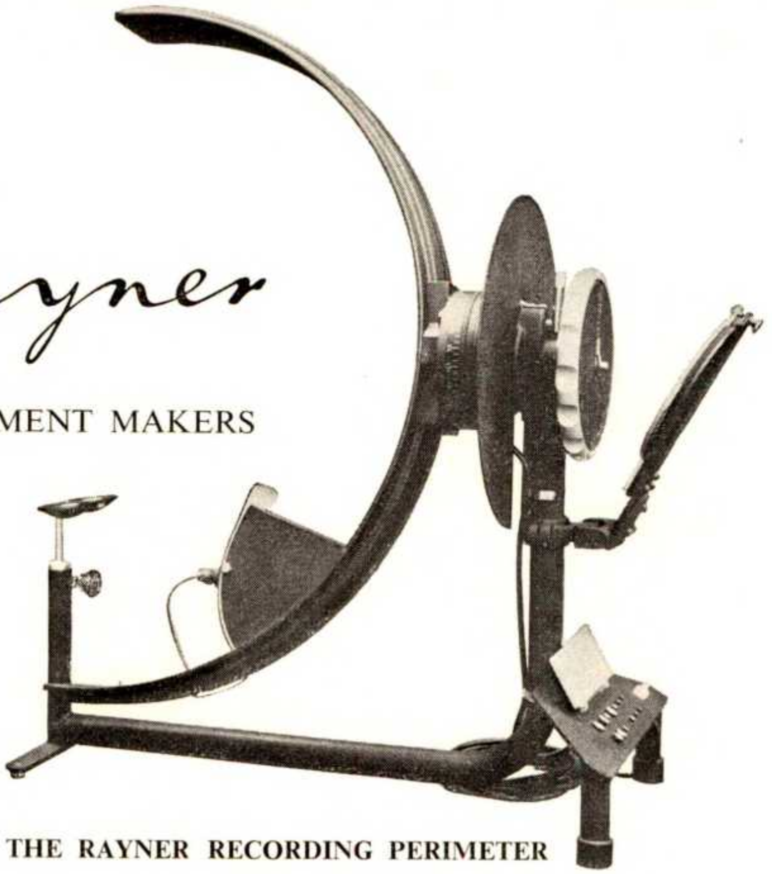

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UNIVER

Communications

Profile of presenting states of eyes in angle-closure glaucoma

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From the Department of Ophthalmology, University of Manchester, and Manchester Royal Eye Hospital

It seems to be often believed that most cases of closed-angle glaucoma present in the acute state, while chronic cases are uncommon. It was our impression that chronic closed-angle glaucoma as a presenting state is quite frequent and also that it accounts for a high proportion of patients with apparently unilateral glaucoma, *i.e.* one eye having pathological cupping of the disc and raised ocular tension, the other eye having a normal optic disc and ocular tension.

Our interest in this subject also arose because occlusion of the central retinal vein and thrombotic glaucoma were found in some patients to be associated with closed-angle glaucoma. (Their connection with open-angle glaucoma is well known.) Thrombotic glaucoma is often difficult to distinguish from absolute closed-angle glaucoma, but in both conditions the fellow eye usually provides an important clue to the diagnosis.

An assessment was therefore made of the state of presenting and fellow eyes of 77 patients with closed-angle glaucoma; these were all the new patients who presented with this diagnosis to the Professorial Unit of Manchester Royal Eye Hospital between January, 1966, and July, 1969. We consider that the frequency distribution of types to be presented is probably a representative sample, because only two patients with this particular disease were referred from other consultant surgeons: one had bilateral and the other unilateral chronic closed-angle glaucoma.

The criteria mentioned in the classification below are often not absolute so that some overlap between categories must be admitted. Arabic numerals are used to present eyes and corresponding roman numerals to present fellow eyes.

(1) and (*i*) *Acute and subacute closed-angle glaucoma* Constant features were ocular pain, raised ocular tension, corneal oedema, and shallow anterior chamber.

(2) and (*ii*) *Chronic closed-angle glaucoma* Raised ocular tension (> 21 mm. Hg) and gonioscopically closed angles were invariably present. Ocular pain and corneal oedema were either absent or minimal.

(3) and (*iii*) *Intermittent angle-closure glaucoma* Symptoms of recurrent blurring of vision and "glaucomatous" haloes were present, but at the time of examination the ocular tension was normal and the angles of the anterior chambers were open but narrow and predisposed to angle-closure.

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(4) and (*iv*) *Angle-closure glaucoma associated with*

(*a*) Central or tributary retinal vein occlusion

(*b*) Thrombotic glaucoma

(*c*) Absolute closed-angle glaucoma

These three conditions have been included together because it is often very difficult to differentiate (*b*) from (*c*), while of course (*b*) is necessarily associated with (*a*).

(5) and (*v*) *Angle-closure induced by mydriatic eye drops*

(6) and (*vi*) *Asymptomatic but judged to be predisposed to angle closure on gonioscopy, e.g.* "fellow eyes" with no symptoms and normal ocular tension.

(7) and (*vii*) *Asymptomatic and considered normal*

Results and comments

The state of presenting and fellow eyes in the 77 patients included in this survey is recorded in Table I. The Figure shows the frequency of the various types of closed-angle glaucoma in presenting eyes. Females (58 or 75·3 per cent.) outnumbered males (19 or 24·7 per cent.). Duke-Elder (1969) mentions that closed-angle glaucoma is commoner in females. Surprisingly, the average age of the males was 58·8 years and that of the females 67·6 years.

(1) *Acute and subacute closed-angle glaucoma in:*

(A) PRESENTING EYES

These comprised surprisingly only 39 (50·6 per cent.) of the 77 cases. There were fewer males (8) than females (31); difference significant at $P<0{\cdot}001$ using the Sign test (Siegel,

Table I

Type of closed-angle glaucoma	*Eyes*						
	Presenting				*Fellow*		
	Sex				(*i*)	(*ii*)	(*iii*)
	Male	*Female*	*Total* *No.*	*Total* *Per cent.*	*Acute and subacute*	*Chronic*	*Intermittent*
(1) Acute and subacute	8	31	39	50·6	3	5	0
(2) Chronic	8	16	24	31·2	0	12	0
(3) Intermittent	0	6	6	7·8	0	0	0
(4) Associated with central retinal vein occlusion ± thrombotic glaucoma or absolute closed-angle glaucoma	3	2	5	6·5	0	1	0
(5) Induced by mydriatic eye drops	0	3	3	3·9	0	0	0
Total	19	58	77	100	3 (3·9%)	18 (23·4%)	0

"Fellow eyes" in Groups (*i*) to (*vii*) correspond by horizontal rows to their contralateral "presenting eyes" str

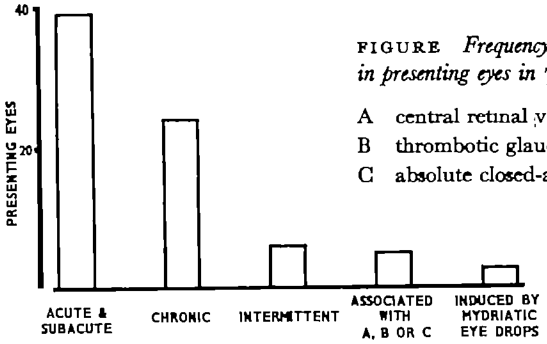

FIGURE *Frequency of different types of closed-angle glaucoma in presenting eyes in 77 patients:*

A central retinal vein occlusion
B thrombotic glaucoma
C absolute closed-angle glaucoma

1956). Rather unexpectedly, the males were younger than the females; the mean age of males was 55·4 and that of females 70·9 years, and this difference was significant at P = 0·0023, using a Mann-Whitney U test (Siegel, 1956).

(B) FELLOW EYES

The state of the fellow eye (classified as in Table I) in the 39 cases of acute closed-angle glaucoma in the presenting eye was as follows:

(*iii*), (*v*), and (*vii*) None.

(*i*) Acute closed-angle glaucoma 3
i.e. three had bilateral acute closed-angle glaucoma

(*ii*) Chronic closed-angle glaucoma 5
These five fellow eyes would not have been suitable for prophylactic peripheral iridectomy

ciated with al retinal occlusion, nbotic, or lute glaucoma	(*v*) *Induced by mydriatic eye drops*	(*vi*) *Asymptomatic or predisposed*	(*vii*) *Normal*	*Total*	
				No.	*Per cent.*
	0	28	0	39	50·6
	0	11	1	24	31·2
	0	6	0	6	7·8
	0	4	0	5	6·5
	3	0	0	3	3·9
%)	3 (3·9%)	49 (63·6%)	1 (1·3%)	77	100

ording to Groups 1 to 5

Table II *State of optic discs and ocular tension in 24 cases of chronic closed-angle glaucoma in the presenting eye*

Eyes of 24 patients		*Presenting* (24)	*Fellow* (24)	*Asymmetrical cases*
Optic disc	Pathological cupping	21	9	* 12 (50%)
	Normal	3	15	
Ocular tension	Raised (*i.e.* >21 mm. Hg)	24	11	** 13 (54·2%)
	Normal (*i.e.* 21 mm.Hg or less)	0	13	

*presented with one pathologically cupped disc and one normal disc
**presented with raised ocular tension (>21 mm.Hg) in one eye and normal ocular tension (21 mm.Hg or less) in the other

(*iv*) Angle closure associated with central retinal vein occlusion and:

Thrombotic glaucoma	1
Absolute closed-angle glaucoma	2

The three patients in Group (*iv*) all had symptoms in these "fellow" eyes (for 3 years, one month, and many years respectively) before the acute attack in the presenting eye developed and eventually caused them to attend an ophthalmologist. If the severe visual disturbance in what is now classified as the "fellow" eye had not been ignored, the acute attack in the "presenting "eye could have been prevented, because tonometry, gonioscopy, and provocative tests would probably have revealed a predisposition to angle closure.

(*vi*) Asymptomatic but judged to be predisposed to angle closure on gonioscopy 28

Without prophylactic peripheral iridectomy, the liability to signs or symptoms in fellow eyes over a period of 5 years is about 40 to 60 per cent. (Winter, 1955; Bain, 1957; Lowe, 1962; Becker and Shaffer, 1965).

(2) *Chronic closed-angle glaucoma in:*

(A) PRESENTING EYES

A surprisingly high number, 24 (31·2 per cent.) were in this group. This emphasizes the importance of gonioscopy which is so essential a part of the examination of both eyes of a patient with glaucoma or raised ocular tension at the first visit.

(B) FELLOW EYES

The state of the fellow eye in these 24 patients with chronic closed-angle glaucoma in the presenting eye was as follows:

(*i*), (*iii*), (*iv*), and (*v*) None.

(*ii*) Chronic closed angle glaucoma 12
i.e. there were twelve cases of bilateral chronic closed-angle glaucoma.

(*vi*) Asymptomatic but judged predisposed to angle closure 11
These required prophylactic peripheral iridectomy.

(*vii*) Asymptomatic and normal 1

The last patient, a most unusual one indeed, did not require prophylactic peripheral iridectomy. Measurement of ocular dimensions in both eyes of this patient showed surprisingly little asymmetry:

Measurements	*Presenting eye*	*Unaffected fellow eye*
Corneal diameter (mm.)	10·71	10·51
Corneal thickness (mm.)	0·61	0·63
Corneal radius	7·54 at 10° 8·10 at 100°	7·70 at 170° 8 16 at 82·5°
Corneal astigmatism	0·56 against the rule	0·46 against the rule
Anterior chamber depth (mm.)	2·34	2·43
Lens thickness (mm.)	4·54	4·33
Vitreous length (mm.)	14·27	13·79
Axial length (mm.)	21·76	21·18
Refraction	+2·75 D sph., +5 D cyl., axis 5°	+3·75 D sph., +3·75 D cyl., axis 175°

However, 2 years later this apparently normal fellow eye was reclassified, on gonioscopic appearances of a narrow angle and iris bombé, as predisposed to closed-angle glaucoma and a prophylactic peripheral iridectomy was done. Perhaps a critical amount of forward displacement of the anterior surface of the lens is required before "significant" iris bombé results.

Table II shows the state of the optic discs and ocular tensions in the 24 patients who had chronic closed-angle glaucoma in the presenting eye. Half of the 24 patients had pathological cupping of the disc in the presenting eye and a normal disc in the fellow eye. This is a higher incidence of a greater degree of asymmetry than that observed by Fishman (1970) in ocular hypertension and in open-angle glaucoma (30 and 36 per cent.) compared with normal (5·6 per cent.): Fishman also mentions two cases of asymmetrical cupping in subacute angle-closure glaucoma with early field loss. The ocular tension was raised in all presenting eyes and in only three of them was the optic disc normal, indicating the advanced state of the majority of cases of chronic closed-angle glaucoma at the time of presentation. In only one patient with chronic closed-angle glaucoma and pathological cupping in the presenting eye did the angle open completely on gutt. pilocarpine, indicating that angle closure was not usually reversible (Foulds and Phillips, 1957). Eleven of the fellow eyes had raised ocular tension when first seen and eight of them had pathological cupping of the disc; thirteen fellow eyes had normal ocular tension, *i.e.* 21 mm.Hg or less, and twelve of them had a normal disc. (Eleven were judged on gonioscopy to be predisposed to angle closure and one was normal). Very surprisingly one had normal ocular tension with an open but narrow angle, yet there was pathological cupping of the disc. This fellow eye could well have been diagnosed as a case of "low tension" glaucoma, but raised ocular tension, a closed angle, and pathological cupping of the disc were found in the presenting eye. Presumably irido-trabecular contact had existed for months or years but for some reason had resolved (Foulds and Phillips, 1957).

(3) *Intermittent angle-closure glaucoma in:*

(A) PRESENTING EYES

There were six patients (7·8 per cent.) in this group. They all required prophylactic peripheral iridectomy. The diagnosis may be sufficiently in doubt for provocative tests to be undertaken. A most important feature of the history is that haloes are not present every evening (*cf.* lenticular haloes) and that they are usually associated with pain, a combination which is a useful diagnostic feature.

(B) FELLOW EYES

The state of the fellow eye in these six patients with intermittent angle-closure glaucoma was as follows:

(*i*)—(*v*) and (*vii*) None.

(*vi*) Asymptomatic but predisposed to angle closure 6
These all required prophylactic peripheral iridectomy

(4) *Angle-closure glaucoma associated with:*

Central retinal vein occlusion	1
Thrombotic glaucoma	1
Absolute closed-angle glaucoma	3

(A) PRESENTING EYES

The one case of central retinal vein occlusion required prophylactic peripheral iridectomy. The presenting eye of the patient with thrombotic glaucoma was enucleated. All three presenting eyes affected with absolute closed-angle glaucoma had become completely blind.

(B) FELLOW EYES

The state of the fellow eyes in this group was as follows:

(*i*), (*iii*–*v*), and (*vii*) None.

(*ii*) Chronic closed-angle glaucoma 1

(*vi*) Asymptomatic but predisposed to angle closure 4

The risk of closed-angle glaucoma in the four latter fellow eyes was probably eliminated by peripheral iridectomy. The group of 39 patients with acute closed-angle glaucoma in the presenting eye included three in which the fellow eye had previously suffered thrombotic glaucoma (1 case) and absolute closed-angle glaucoma (2 cases). If these patients had presented at the onset of symptoms in what is now classified as the "fellow eye", the acute angle-closure attack in the presenting eye, which eventually led them to attend an ophthalmologist, could have been prevented by peripheral iridectomy. Although these patients form a small proportion of those presenting with closed-angle glaucoma, they are intrinsically interesting and each one represents a potential diagnostic pitfall unless gonioscopy is done on both eyes on all patients presenting with central or tributary retinal vein occlusions, thrombotic glaucoma, and so-called absolute glaucoma.

That central or tributary retinal vein occlusion may be a presenting symptom or sign of closed-angle glaucoma or intermittent angle closure glaucoma is often forgotten, and this diagnosis should be considered even when ocular tension is "normal"; *i.e.* all these patients should have gonioscopy no matter what the ocular tension. The fellow eye should of course also be examined with equal care.

Even more easily missed is a true "thrombotic" glaucoma initiated by a central retinal vein occlusion which in turn was caused by transient angle closure or a chronically closed-angle. In such cases the fellow eye will usually provide the clue to the underlying diagnosis.

Still more important may be chronic closed-angle glaucoma with corneal oedema and hyperaemia of conjunctival and scleral vessels which can easily masquerade as a thrombotic glaucoma; again, the examination of the fellow eye is important, but careful assessment of the presenting eye, especially careful gonioscopy (in which true new vessels in the angle are not seen), will usually indicate the diagnosis. Although no such case was found in the present series, two patients with this condition had been seen in previous years. Sector iridectomy was safely performed in them and, although the sightless eyes remained hypertensive, the intraocular pressure was lowered and the onset of degenerative changes due to very high pressure may well have been postponed. Prophylactic peripheral iridectomy in the fellow eyes was of course the more valuable by-product of the careful evaluation of these patients.

A diagnosis of "absolute glaucoma" should always be qualified where possible by either "open angle" or "closed angle". We would emphasize that gonioscopy, even of a blind eye, is worth while, as well as in the fellow eye which may be predisposed to angle closure and require prophylactic peripheral iridectomy. The three cases of absolute closed-angle glaucoma in the presenting eye included in this series illustrate this point well. All three eyes were blind and the fellow eye was judged to be predisposed to angle closure in two cases and chronic closed-angle glaucoma was present in the third.

(5) *Angle closure induced by mydriatic eye drops in:*

(A) PRESENTING EYES

This group comprised three patients who all had bilateral closed-angle glaucoma. In two cases gutt. homatropine had been instilled into both eyes by an ophthalmologist. The third was an asymptomatic sister of a patient with closed-angle glaucoma who was given a gutt. eucatropine 5 per cent. water-drinking tonography test as part of a survey of relatives of patients with closed-angle glaucoma.

(B) FELLOW EYES

As mentioned above, all three patients in this group were bilaterally affected.

Iridoschisis This was present bilaterally in one patient, one eye having had an acute closed-angle attack: the other eye was judged to be predisposed to angle closure.

Iridocyclitis No case of closed-angle glaucoma was found which had been mistaken for iridocyclitis with secondary glaucoma. This pitfall is liable to occur occasionally when cells are seen in the anterior chamber, the possibility of closed-angle glaucoma unfortunately may not be considered and gonioscopy may be omitted.

No case of self-limiting disease (Phillips and Woodhouse, 1963) was found.

Summary

A survey was made of 77 patients with closed-angle glaucoma who presented to the Professorial Unit of the Manchester Royal Eye Hospital between January, 1966, and July, 1969. Females (75·3 per cent.) outnumbered males (24·7 per cent).

Only 39 (50·6 per cent.) had acute closed-angle glaucoma in the presenting eye; of these eight were males and 31 females (difference significant at $P<0{\cdot}001$). The average age of the males was 55·4 years and of the females 70·9 years (difference significant at $P = 0{\cdot}0023$).

Surprisingly, 24 (31·2 per cent.) had chronic closed-angle glaucoma in the presenting eye. Eleven of these were bilaterally affected with raised ocular tension (>21 mm. Hg) and closed angles in both eyes. Pathological cupping of the optic discs was seen in 21 presenting and 9 fellow eyes.

In presenting eyes, central retinal vein occlusion was found in one, thrombotic glaucoma in one, and absolute closed-angle glaucoma in three. The fellow eye in these five patients was found on gonioscopy to be predisposed to angle closure in four cases, while chronic closed-angle glaucoma was present in the fifth. Of 39 patients with acute closed-angle glaucoma in the presenting eye, one had central retinal vein occlusion associated with thrombotic glaucoma, and two had absolute closed-angle glaucoma in the fellow eye; these three patients had apparently ignored the symptoms in the "fellow" eyes.

Careful assessment of both eyes (N.B. the fellow as well as the presenting eye) by tonometry and gonioscopy must therefore be done in all cases of glaucoma or suspected glaucoma even when the ocular tension is normal, and in all cases of central (and tributary) retinal vein occlusion and thrombotic glaucoma. A careful differentiation between thrombotic glaucoma and chronic closed-angle glaucoma is important. Absolute glaucoma should be subdivided into open-angle and closed-angle types.

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Conjunctival swabbing for the isolation of TRIC agent *(Chlamydia)*

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Conjunctival scraping has been the standard method of collection of specimens for isolation of TRIC agent.* However, in spite of good instrumentation, even in the hands of experienced workers, conjunctival scraping commonly causes moderate or severe irritation, some bleeding, and conjunctival reaction, especially in acute or subacute conjunctivitis, and intensifies the patient's discomfort. It is therefore desirable to find an alternative and simpler method which would ensure a proper collection of specimens with minimal harm to tissues.

Swabbing the conjunctiva has been used for isolation of TRIC agent by Tang, Huang, Chang, and Wong (1957, 1958), Collier and Sowa (1958), Collier, Duke-Elder, and Jones (1958), and Gear, Cuthbertson, and Ryan (1967), but the technique has not come into general use.

The purpose of this study was to investigate the efficiency of swabbing for the collection of specimens from the conjunctiva for the isolation of TRIC agent in comparison with a standard technique of scraping.

Methods and materials

SELECTION OF CASES

Specimens used in this study were collected in cases suggestive of TRIC infection of the eye; in some cases TRIC inclusion bodies had already been observed in conjunctival scrapings.

COLLECTION OF SPECIMENS

The conjunctiva was anaesthetized by 3–4 drops of Jocaine (Cocaine hydrochloride 4 g., adrenaline acid tartrate 0·15 g., sod. metabisulphite 0·1 g., neomycin sulphate 0·5 g., chlorhexidine acetate 0·1 per cent. 5 ml., distilled water to 100 ml.).

Scraping Conjunctival scrapings were collected using sterile Kimura platinum spatulas or sterile aluminium scrapers which were flattened at both ends. The collected material was suspended in 1·4 ml. of 2SP medium with antibiotics (M/15 phosphate buffer at pH 7·2 with sucrose 0·2 M, streptomycin 50 μg./ml. and vancomycin 100 μg./ml.) in a screw-capped bottle containing a few glass beads.

Swabbing Conjunctival swabbings were collected with disposable sterile culture swabs (Stayne Laboratories Limited, High Wycombe, Bucks); one dry swab was used for each eye. The conjunctival surface was wiped firmly three or four times; the swab was then placed in a screw-capped bottle containing 2SP with antibiotics and a few glass beads, the stick being broken short.

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*Collier (1959), Hanna, Thygeson, and Jawetz (1959), Jones, Collier, and Smith (1959), Bernkopf, Nishmi, Maythar, and Feltelberg (1959), Perret and Mann (1960), Hanna, Jawetz, Thygeson, and Dawson (1960), Tarizzo (1961), Hanna (1962), Murray, Guerra, Abbott, and McComb (1962), Mordhorst (1964, 1965a, 1965b, 1967), Sowa, Sowa, Collier, and Blyth (1965), Dawson and Schächter (1967), Gordon, Harper, Quan, Treharne, Dwyer, and Garland (1969)

In this study, swabs and scrapings were collected separately from different areas of the conjunctiva, *i.e.* upper tarsus, upper fornix, and lower lid, and each specimen was cultured separately. These specimens were kept at +4°C. for 2 to 3 hrs until transferred on wet ice to the laboratory where they were stored at −70°C. until cultured.

A total of fifty specimens was collected by each method of collection. In 25 cases, swabbings were collected before scrapings; in the remaining 25 cases the order of collection was reversed.

CELL CULTURE

A simplified irradiated McCoy cell culture technique employing a one passage system was used in this study.

Monolayers of irradiated McCoy cells were prepared by the technique of Gordon and others (1969). Clinical specimens were shaken on a Whirlimixer for 1 min. and then subjected to indirect sonication (modified Dawe Soniprobe, Model 1130A, operating at a peak output of 200 W) for 7 min. To this specimen was added 1 ml. of fresh complete medium with additional glucose and antibiotics (CMGA: Gordon and others, 1969). The specimen was inoculated into two tubes containing monolayers of irradiated McCoy cells. The tubes were then centrifuged at 2,700 G. for 1 hr. in a MSE Super Minor Centrifuge.

The medium in the tubes was replaced by fresh CMGA 2 hrs after centrifugation. At approximately 6 hrs after inoculation the medium was removed from one tube, and the cells were washed several times with phosphate buffer and fixed for 10 min. by the addition of methyl alcohol. The monolayers were stained with Giemsa's stain (Gordon and others, 1969).

Using a Zeiss RA microscope, Giemsa-stained coverslips were screened for the presence of inclusion bodies using ×16 objective and optovar ×1·25 with darkfield illumination.

With 35 positive specimens, the number of inclusions in the first tube was estimated by counting the number of inclusions in ten to twenty fields. In the other forty positive specimens, the frequency of inclusions in the first tube was estimated as + to − + + +, *i.e.* + = 1 to 10 inclusions per coverslip, + + = 11 to 100, + + + = 101 to 1,000, and + + + + = over 1,000.

If the first tube was negative, the second tube was fixed and stained with Giesma not later than 72 hrs after inoculation and examined for the presence of inclusions. If the first tube was positive the second was harvested and stored for further studies.

Close attention was given to the prevention of accidental cross-infection between specimens (Gordon and others, 1969). One coded uninfected dummy isolation specimen was included at irregular intervals as a control for every ten specimens.

Results

Positivity of cultures of material collected by swabbing or scraping

Of fifty specimens collected by scraping, 37 (74 per cent.) were positive in cell culture for *Chlamydia:* of fifty specimens collected by swabbing, 38 (76 per cent.) were positive (Table I).

Table I *Results of cultivation of swabbings and of scrapings of the conjunctiva for the isolation of* TRIC *agent*

No. of specimens		*Positive*			
		By swabbing		*By scraping*	
		No.	*Per cent.*	*No.*	*Per cent.*
Swabbing first	25	25	100	25	100
Scraping first	25	13	52	12	48
Total	50	38	76	37	74

Positivity in relation to the order in which specimens were collected

During the first section of this study swabbings were collected before scrapings; this series of cases included many that were already known to be inclusion positive and there was an overall high rate of positivity. Thus all of 25 swabbings collected before scrapings were positive and all of 25 scrapings collected after swabbing were also positive.

During the second section of this study scrapings were collected before swabbings. In this series of less selected cases twelve out of 25 scrapings collected before swabbing were positive and thirteen of the swabbings collected after scraping were also positive (Table I). Thus the second collection was just as often positive regardless of whether the first collection was by scraping or swabbing.

Number of inclusions in first passage in cell culture

The number of inclusions detected in cells inoculated with material collected by swabbing, compared with those detected in cells inoculated with material collected by scraping, is shown in Table II. In each case more inclusions were present in the culture inoculated with swabbings. In the five cases in which swabbings were collected first, the total yield of inclusions by swabbing was 1,503 as compared with 95 inclusions by scraping (Table II). In the other twenty positive cases in this group, in which the frequency of inclusions was recorded as + to ++++, the yield by swabbing was always + to ++ higher than that by scraping. In thirteen positive cases in which swabbing was collected after scraping, the total yield of inclusions by swabbing was 39,776 as compared with 10,625 by scraping (Table II).

Table II *Number of inclusions in cell cultures inoculated with either swabbings or scrapings of conjunctiva*

Cell culture code number	*No. of inclusions**			*Order of collection*
	Swabbings	*Scrapings*	*Ratio swabbing/scraping*	
1398–1399	65	2	30 : 1	Swabbing first
1400–1401	1,000	27	30 : 1	
1402–1403	252	8	30 : 1	
1406–1407	104	16	5 : 1	
1408–1409	82	42	2 : 1	
Total	1,503	95		
1683–1684	7	0	—	Scraping first
1705–1706	610	400	1·5 : 1	
1716–1717	630	160	4 : 1	
1718–1719	9	4	2 : 1	
1754–1755	3,500	1,600	2 : 1	
1756–1757	3,260	600	5 : 1	
1758–1759	4,100	860	5 : 1	
1762–1763	2,720	1,720	1·5 : 1	
1764–1765	4,140	1,320	3 : 1	
1766–1767	5,600	1,320	4 : 1	
1746–1747	600	8	75 : 1	
1748–1749	1,600	33	50 : 1	
1750–1751	13,000	2,600	5 : 1	
Total	39,776	10,625		

* Number of inclusions in one cell culture monolayer at first passage

Discussion

In view of the 4-fold number of inclusion bodies found in cultures inoculated with material collected by swabbing (41,279) as compared with material collected by scraping (10,720), it is surprising that there was so little superiority of swabbing over scraping when compared on the basis of the number of positives (38: 37), even though each pair of specimens compared came from only one area of conjunctiva of one eye, *viz.* upper tarsus, upper fornix, or lower lid. Presumably, however, the collection of material from cases that had less viable TRIC agent in the conjunctiva would show a greater superiority for swabbing. It is of interest that, regardless of the order of collection by swabbing or scraping, the second specimen was just as often positive as the first.

These findings would appear to indicate that in isolation-positive cases in London, there is generally enough viable TRIC agent in the conjunctiva to yield positive specimens if collection is immediately repeated. But counting or estimating the number of inclusions in the first passage in primary isolation in McCoy cells provides a more revealing method of assessing the quantity of viable agent collected from the conjunctiva than does a comparison of the prevalence of positive cultures.

Conjunctival scraping for collection of material has the following disadvantages:—

(1) An experienced collector is essential for the collection of good specimens.

(2) The use of scrapers that are damaged or of poor quality will result in the collection of poor specimens, and may increase the reaction in the eye.

(3) The process of sterilization of scrapers, collection of scrapings, and cleaning of scrapers is relatively slow and complicated, taking approximately 5 minutes per patient.

(4) In acute or subacute conjunctivitis, bleeding is a common complication of scraping. The bleeding may affect the quality of the specimen and lead to neutralization of infectivity by serum antibodies.

(5) Reactions after scraping include mild or severe irritation, pain, lacrimation, photophobia, swelling of the lids, conjunctival hyperaemia and discharge, and occasionally the development of inflammatory conjunctival membranes. These side-effects often discourage patients from co-operating in serial scraping for follow-up studies or tests of cure.

(6) The term "scraping" often leads to fear and antagonism in the patient.

In this study is has been shown that conjunctival swabbing is at least as sensitive as scraping for the detection of positive cases, and the amount of cultivable TRIC agent in swabbings is greater than that in scrapings.

The other advantages of swabbing are:

(1) Simple instruction enables a relatively inexperienced technician or nurse to collect good specimens for isolation.

(2) The use of commercially available swabs provides a simple and rapid method of specimen collection that takes approximately only 1 minute per patient.

(3) Swabbing rarely gives rise to bleeding.

(4) Conjunctival reaction to swabbing is minimal and consists of slight soreness and irritation of short duration.

(5) The term "swabbing" does not frighten the patient.

The commercial swabs used in this study measured 10–12 mm. by 5–7 mm. with a rounded end, and were firmly fixed on the end of wooden sticks. This size of swab usually absorbs 0·2 to 0·3 ml. of medium. The blunt end of the swab is important for the collection of specimens from the conjunctiva of the lower lid. It has been shown that swabs that have been overheated, especially in the hot-air oven, may char and give rise to tar-like products which are toxic to bacteria and may be toxic to *Chlamydia;* swabs for these collections should therefore be sterilized by radiation or by autoclaving (Cruickshank, 1965).

In view of all these advantages of swabbing over scraping there would seem little doubt that swabbing is the method of choice. Its adoption should significantly reduce the work involved and the discomfort sustained by the patient in the isolation of TRIC agent from the eye in field studies of trachoma or in diagnostic clinics for external diseases of the eye.

Summary

In this study, swabbing of the conjunctiva for the collection of specimens for the isolation of chlamydial agents was compared with a standard technique of scraping.

Fifty specimens collected by each method were inoculated into cell monolayers using a simplified system of irradiated McCoy cell culture; 37 (74 per cent.) were positive in specimens collected by scraping and 38 (76 per cent.) in specimens collected by swabbing. The number of inclusion bodies detected in cell culture was approximately 4-fold higher from specimens collected by swabbing than from those collected by scraping.

The simplicity and speed of collection by swabbing, with freedom from the undesirable sequelae of scraping, should significantly facilitate the use of isolation of TRIC agent in field studies of trachoma, and simplify the work of diagnostic clinics for external diseases of the eye.

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Isolation of TRIC agent *(Chlamydia)* in irradiated McCoy cell culture from endemic trachoma in field studies in Iran

Comparison with other laboratory tests for detection of *Chlamydia**

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The technique of cultivation of TRIC agent, and other *Chlamydia* (*Bedsonia*) by centrifugation onto irradiated McCoy cells, developed by Gordon, Magruder, Quan, and Arm (1963), Magruder, Gordon, Quan, and Dressler (1963), and Gordon, Dressler, and Quan (1967), has been used to recover laboratory-adapted isolates of TRIC agent from the infected eyes of simians (Gordon and others, 1963) and of man (Magruder and others, 1963).

Studies recently completed in this laboratory on clinical specimens from genital or genitally-related ocular infections in London showed that isolation in irradiated McCoy cells is more sensitive for the detection and isolation of chlamydial agents than cultivation in the yolk sac of embryonated hen's eggs or inclusion-finding in Giemsa-stained scrapings (Gordon, Harper, Quan, Treharne, Dwyer, and Garland, 1969; Dunlop, Hare, Darougar, Jones, and Rice, 1969). It was also shown that TRIC agent could be isolated in the cell culture system from endemic trachoma in Iran, but the number of specimens tested was too small to give an assessment of the sensitivities of the two methods of isolation in relation to the finding of inclusions in conjunctival scrapings.

Isolates of TRIC agent from endemic trachoma in the Middle East and the Far East have shown biological differences from TRIC isolates of genital origin in London, USA, and Taiwan (Alexander, Wang, and Grayston, 1967; McComb and Bell, 1967; Wang and Grayston, 1970, 1971). It was, therefore, not clear whether the irradiated McCoy cell system could provide a satisfactory alternative to the yolk sac of embryonated hen's eggs for isolation of TRIC agent from endemic trachoma.

This paper compares the results of isolation of TRIC agent in cell culture with those of isolation in the yolk sac of embryonated eggs from scrapings collected during a field study of trachoma in certain villages in Iran. It also relates these isolations to the findings of inclusions in conjunctival scrapings stained by iodine or Giemsa stain, and the results of microimmunofluorescence typing of the isolates.

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*This investigation was carried out as a collaborative study by workers of the School of Public Health, University of Teheran, and the Institute of Ophthalmology, University of London

Material and methods

SELECTION OF CASES

Specimens used in this project were collected during a field survey in Iran in May, 1967, from four villages: Baba Rais, Varchagh, and Galeh Asad in the Malayer area, and Daylam Sofla in the Dezful area.

Clinical examinations were carried out in a field station using a modified Haag-Streit slit lamp microscope for the cornea, tarsal conjunctiva, and lower fornix, and Keeler ×2·5 telescopic spectacles with integrated illuminator for the upper fornix of the conjunctiva.

Of 49 cases selected for this project, 46 had clinical signs of active trachoma (43 children and 3 adults). The clinical picture and the intensity of signs of disease in these patients will be described and discussed in subsequent papers. The other three patients were babies between 3 and 6 months of age with acute papillary conjunctivitis.

CONJUNCTIVAL SCRAPINGS

The conjunctiva of each eye was anaesthetized by two or three drops of Jocaine N (cocaine hydrochloride 4 g., adrenalin acid tartrate 0·18 g., sod. metabisulphite 0·1 g., neomycin sulphate 0·5 g., chlorhexidine acetate 0·1 per cent., 5 ml. distilled water to 100 ml.). Smears for detection of inclusion bodies were prepared from the conjunctiva of the left eye. In this survey the conjunctiva was divided into four different areas: upper tarsus, upper border of upper tarsus, upper fornix, and lower lid (including both lower tarsus and fornix). Conjunctival scrapings were collected from each area with sterile aluminium scrapers which were flattened at both ends. This material was placed on slides that had been marked by diamond pencil with circles 6 mm. in diameter: one circle for each area of the conjunctiva. Smears collected from each of 49 patients were fixed with methyl alcohol for 10 min., dried, and kept at room temperature until stained by iodine solution and subsequently by Giemsa stain.

SPECIMENS FOR ISOLATION

Material was collected from the anaesthetized right eye of each of the 49 patients. Conjunctival scrapings were taken from each of the four areas in turn, and were placed in a single vial as a combined specimen.

Conjunctival scrapings collected from 24 cases in three of the villages, Baba Rais, Varchagh, and Galeh Asad, were suspended in 2·4 ml. 2SP medium with antibiotics (M/15 phosphate buffer at pH 7·2 with 0·2M sucrose, 50 μg./ml. streptomycin, and 100 μg./ml. vancomycin). The specimens were kept for 6 to 7 hrs on wet ice or in a +4°C refrigerator until they were ampouled and stored in a Linde liquid nitrogen refrigerator at −180°C. Another 25 specimens from the village of Daylam Sofla were collected in 1·5 ml. SPG (Bovarnick, Miller, and Snyder, 1950), containing 20,000 μg./ml. streptomycin and 20,000 u./ml. neomycin. These specimens were kept at +4°C. for about 24 hrs until they were ampouled and stored in the liquid nitrogen refrigerator for 4 to 10 mths before cultivation.

CELL CULTURE AND YOLK SAC CULTIVATION OF *CHLAMYDIA*

The technique for cell culture and for culture in embryonated eggs were those of Gordon and others (1969).

MICROIMMUNOFLUORESCENCE TYPING OF ISOLATES

The isolates that had been stored in this study were subsequently typed using the microimmunofluorescence test (micro-IF test) described by Wang and Grayston (1970, 1971) and confirmed by Treharne, Katzenelson, Davey, and Gray (1971).

DETECTION OF INCLUSIONS IN CONJUNCTIVAL SCRAPINGS

Iodine staining Smears previously fixed with methyl alcohol were stained with Lugol's solution (Iodine 1 g., potassium iodide 2 g., water 100 ml.) for 10 min. Slides were rinsed in water and dried with blotting paper, since it has been our experience, confirmed by other workers (Schachter and Meyer, 1969), that rinsing in water washes out excess iodine and prevents crystallization without interfering with the staining of inclusions. The smear in each circle was examined for 5 to 10 min., using an oil immersion objective ×40 and ×8 oculars; the number of inclusions was recorded. Smears that were heavily blood-stained were treated with 0·5 per cent. ammonia solution before staining with iodine (Sowa, Sowa, Collier, and Blyth, 1965).

Giemsa staining After examination, smears stained with iodine were decolourized by immersion in methyl alcohol overnight. They were then stained with 10 per cent. Giemsa solution for 1 hr. The smear in each circle was examined for 15 to 20 minutes, using an oil immersion objective ×40 and ×8 oculars; the number of inclusions was recorded.

Results

Isolation of TRIC *agent in cell culture*

PRIMARY ISOLATION IN CELL CULTURE

Of 49 specimens inoculated into cell cultures, thirteen produced typical inclusion bodies in infected cells (Table I; Figs 1 and 2, overleaf). All thirteen isolates produced inclusions that stained with iodine (Fig. 3, overleaf), thus establishing that they were subgroup A *Chlamydia* (Gordon and Quan, 1965).

Table I *Incidence of positives among 49 cases of trachoma or conjunctivitis in certain villages in Iran, by various methods of detecting Chlamydia*

Source of specimens	*No. of specimens*	*Isolation*				*Conjunctival inclusions*				*Total positive by any method*	
		Cell culture		*Egg culture*		*Giemsa stain**		*Iodine stain**			
		+	*Per cent.*	+	*Per cent.*	+	*Per cent.*	+	*Per cent.*	+	*Per cent.*
Trachoma											
Stage I	18	6	33·3	1	5·5	2	11·1	4	22·2	7	39
Stage II	17	5	29·4	1	5·8	3	17 6	1	5·8	7	41·1
Stage III	11	2	18·1	2	18	1	9	1	9	4	36·3
Total	46	13	28·2	4	8·6	6	13	6	13	18	39·1
Conjunctivitis	3	0	0	0	0	0	0	0	0	0	0

*All four areas of conjunctiva examined, see text
+ = Positive

Of the total of thirteen positives in cell culture isolation, only six were also positive by one or more other methods of detecting *Chlamydia* (Table II, overleaf).

Cells inoculated with the specimens from Daylam Sofla, that had been collected in the higher concentration of antibiotics, developed intracytoplasmic granules. This granulation caused difficulty in identifying inclusion bodies in the first passage, but was not transmitted to subsequent passages. However, the rate of contamination with bacteria was very low throughout this study (one specimen in second passage and another specimen in third passage were contaminated). All cell cultures inoculated with coded uninfected control specimens remained negative through three passages.

Table II *Distribution of positive results using different methods of detection of Chlamydia*

Specimen code	*Stage of trachoma*	*Isolation*		*Conjunctival inclusions*	
		Cell culture	*Egg culture*	*Iodine stain*	*Giemsa stain*
271B*	I	+	−	−	−
100V*	I	+	−	+	−
102V	I	+	+	+	+
269V	I	+	−	−	−
25D*	I	+	−	−	−
28D	I	−	−	+	−
64D	I	+	−	+	+
36A*	II	−	−	+	+
297B	II	+	−	−	−
299B	II	+	−	−	−
20V	II	−	+	−	−
114V	II	+	−	−	+
227V	II	+	−	−	+
14D	II	+	−	−	−
72A	III	−	+	−	−
174V	III	−	+	−	−
68D	III	+	−	−	+
94D	III	+	−	−	−
Total 18		13	4	6	6

*A = Village of Galeh Asad (Malayer area)
B = Village of Baba Rais (Malayer area)
V = Village of Varchagh (Malayer area)
D = Village of Daylam Sofla (Dezful area)
+ = Positive
− = Negative

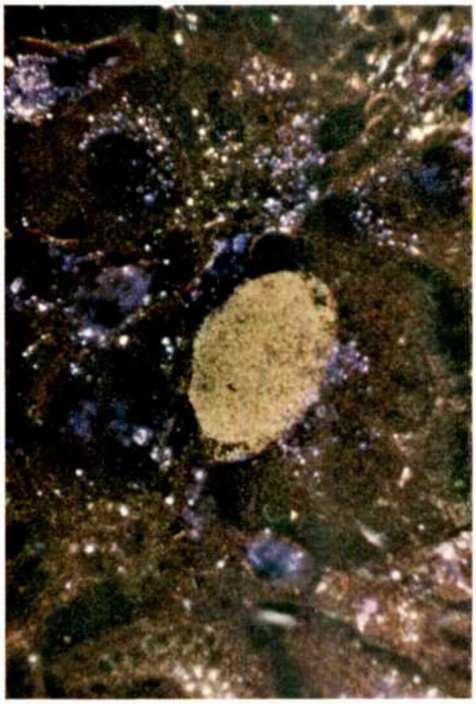
SERIAL PASSAGE OF ISOLATES IN IRRADIATED McCOY CELLS

Six of the thirteen chlamydial agents isolated in cell culture were stored at the time of isolation: five of these were revived and serial passage in irradiated cells was subsequently attempted. At each passage the harvested cell suspension was sonicated and diluted with CMGA (Gordon and others, 1969) to contain approximately ten to twenty mature inclusions per ml. Of this dilution 1 ml. was inoculated onto each fresh monolayer using the standard technique. All five isolates were passaged successfully six to nine times; the average number of inclusions formed at each passage was 100 to 200 per coverslip, indicating 10–20-fold serial multiplication.

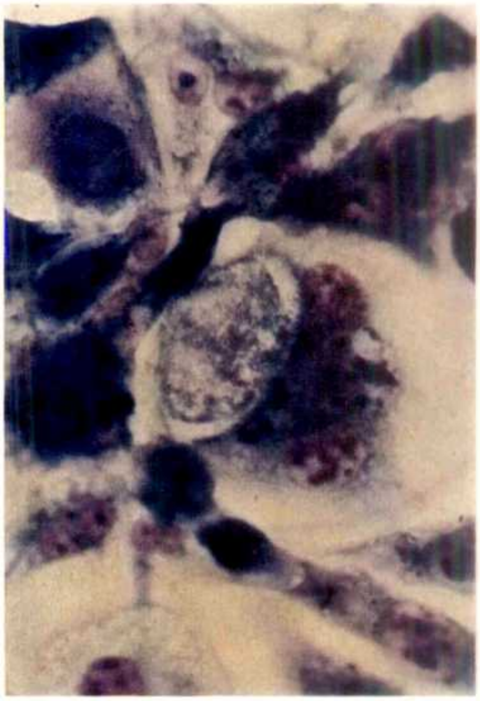
PASSAGE FROM CELL CULTURE TO YOLK SAC

Passage of tissue culture-isolates to the yolk sac of embryonated hen's eggs was attempted with all six of the isolates that had been stored. The cell culture isolate was passaged in McCoy cells until the number of mature inclusions in the harvest reached at least 500 per ml. Of this material 0·3 ml. was inoculated into each of three 7-day-old embryonated hen's eggs. In each case Giemsa-stained smears from harvested yolk sacs of the first passage eggs contained numerous elementary bodies. Thereafter each agent could be propagated by serial passage in the yolk sac without difficulty, and has been available for immunofluorescence typing and other studies.

(1)



(2)



(3)

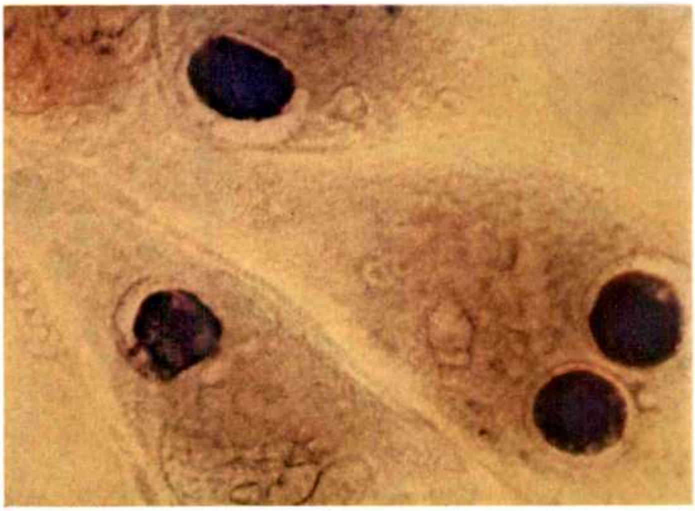


FIG. 1 TRIC *inclusion body in irradiated McCoy cell*, 60 *hrs, Giemsa stain*, × 1280, *darkfield illumination. The elementary bodies show as bright golden fluorescing particles within the inclusion body*

FIG. 2 TRIC *inclusion body in irradiated McCoy cell*, 60 *hrs, Giemsa stain*, × 1280, *bright field illumination (same field as Fig.* 1). *The contrast between the elementary bodies in the inclusion bodies and other material in the monolayer is much less striking than with darkfield illumination*

FIG. 3 TRIC *inclusion bodies in irradiated McCoy cells*, 48 *hrs, iodine stain*, × 1920. *The inclusion bodies, which are typical subgroup A* Chlamydia, *are stained dark brown or mahogany and contrast well with the light yellow background*

Isolation of TRIC *agent in yolk sac*

PRIMARY ISOLATION IN YOLK SAC

Of 49 specimens inoculated into the yolk sac of embryonated eggs, four were shown to be positive by producing typical elementary bodies (Table I).

Of the four positive in egg culture isolation, one was also positive by other methods of detecting *Chlamydia* (Table II).

The rate of contamination with bacteria was very low; only one specimen in the first passage and another specimen in the second passage was contaminated. In eight cases it was not possible to complete three passages because the embryos were undeveloped. In four cases only one passage was completed and in another four cases two passages were completed. All eggs inoculated with coded uninfected control material remained negative throughout three passages.

PASSAGE FROM YOLK SAC TO CELL CULTURE

In order to ascertain whether embryonated eggs might successfully support the growth of some strains of TRIC agent that would not grow readily in McCoy cell cultures, the three yolk sac isolates that were obtained from specimens that did not yield isolates in cell culture were later inoculated into the cell culture system. The isolates from Galeh Asad (72A) produced inclusions in the second passage, the other two specimens from Varchagh (20V and 174V) showed typical inclusions in the first passage in cell culture. There was thus no evidence suggesting selective growth in eggs of any isolate in this series.

MICROIMMUNOFLUORESCENCE TYPING OF ISOLATES

The three isolates obtained only in the yolk sac and the six tissue culture isolates that had been stored were typed in the micro-IF typing test (Table III). With the exception of

Table III *Designation and microimmunofluorescence type of* 16 *isolates in relation to primary isolation in cells or eggs*

Specimen code	*Egg inoculation*	*T.C. inoculation*	*Designation of isolate*	*Micro IF type*
72A*	+	–	TRIC//IR/IOL-223/OT	C
271B*	–	+	TRIC//IR/IOL-231/OT	C
297B	–	+	TRIC//IR/IOL-251/OT	B
299B	–	+	TRIC//IR/IOL-250/OT	ND**
20V*	+	–	TRIC//IR/IOL-225/OT	C
100V	–	+	TRIC//IR/IOL-206/OT	C
102V	+	+	TRIC//IR/IOL-205/OT	C
114V	–	+	TRIC//IR/IOL-227/OT	ND
174V	+	–	TRIC//IR/IOL-234/OT	C
227V	–	+	TRIC//IR/IOL-232/OT	ND
269V	–	+	TRIC//IR/IOL-233/OT	ND
14D*	–	+	TRIC//IR/IOL-235/OT	D
25D	–	+	TRIC//IR/IOL-245/OT	ND
64D	–	+	TRIC//IR/IOL-237/OT	ND
68D	–	+	TRIC//IR/IOL-236/OT	ND
94D	–	+	TRIC//IR/IOL-243/OT	B

*A = Village of Galeh Asad (Malayer area) V = Village of Varchagh (Malayer area)
B = Village of Baba Rais (Malayer area) D = Village of Daylam Sofla (Dezful area)
+ = Positive – = Negative **ND = Not done

14D (TRIC//IR/IOL-235/OT), which serotyped as Type D, all the other isolates from the Malayer and Dezful areas of Iran which were examined serotyped as Type B or C. In order to check the validity of the typing of this isolate 14D, a further aliquot of the stored third passage level culture material was inoculated into eggs and typed in the micro-IF test. Three repeat test typings consistently identified it as Type D.

Inclusions in conjunctival scrapings

IODINE STAIN

By examination of iodine-stained smears from all four areas of the conjunctiva, six out of 49 patients were shown to be positive by demonstration of typical inclusion bodies (Table I). Examination of scrapings from the upper tarsus alone revealed only two positive in these 49 cases.

Of the six positive by iodine stain, four were positive by other methods (Table II), and only three were positive with Giemsa. It should be noted that, in those cases positive only by iodine, the inclusion bodies were detected in the thicker parts of the smears.

GIEMSA STAIN

By examination of Giemsa-stained smears from all four areas of the conjunctiva, six out of 49 patients were shown to be positive by the demonstration of typical inclusion bodies (Table I). Examination of the upper tarsus alone revealed only one positive out of 49 cases.

All six positive by Giemsa stain were also positive by other methods of detecting *Chlamydia* (Table II). Of these cases, two were negative by iodine stain. The inclusion bodies detected by Giemsa in these two cases were immature and contained either initial bodies only or were of early intermediate type particles (pink or red).

The totals of positives for each method of detecting *Chlamydia* shown in Table I indicate that the cell culture system (13 positives) was over three times more sensitive than egg culture (4 positives). This difference is significant at a level of $P < 0{\cdot}02$. Cell culture was also twice as sensitive as finding inclusions by iodine or by Giemsa-staining techniques. This difference is significant at a level of $P < 0{\cdot}10$.

By combining the positive results of different methods of detecting chlamydial infection (Table II), it may be seen that eighteen out of 46 patients with trachoma (39 per cent.) were found to be positive by at least one of the four methods used.

Discussion

In other studies of trachoma carried out in the Malayer area in North-Western Iran an extremely low rate of positivity was found when scrapings from the upper tarsal conjunctiva alone were examined after staining with iodine. In the present study the proportion positive by this method was again very low: in 46 active cases only two such scrapings were positive with iodine and one with Giemsa stain. When additional scrapings from the conjunctiva of the upper border of the upper tarsal plate, from the upper fornix, and from the lower lid were also examined, there were six positives with iodine and six with Giemsa stain. The iodine stain had some advantage in thick areas of the smears, and the Giemsa stain was better for staining immature inclusions.

Inclusion finding with these stains was thus too insensitive a method of demonstrating the presence of TRIC agent in endemic trachoma in North-Western Iran to provide a satisfactory microbiological parameter for the study of the effect of preventive or therapeutic measures. In our laboratory, fluorescent antibody staining of inclusions in conjunctival scrapings has not been found to be more sensitive than Giemsa staining when applied to TRIC infection of the eye in London (Darougar, Dwyer, Treharne, Harper, Garland, and Jones, 1971).

For these reasons we investigated the sensitivity of isolation of TRIC agent from conjunctival scrapings by inoculation into McCoy cell cultures and into embryonated hen's eggs. Even when applied to conjunctival scrapings after 4 to 10 months' storage in liquid nitrogen, the McCoy cell isolation system gave thirteen positives, as compared with two inclusion-positive upper tarsal scrapings and six positives when all areas were examined by iodine or Giemsa. Aliquots of the same conjunctival scrapings gave only four isolations in yolk sac.

The liquid nitrogen refrigerator used in this study offered a very satisfactory means of preservation of clinical specimens in the field where electrical supplies were inadequate, and provided a reliable method for transportation of specimens from the field to the laboratory in London. It may be possible in future investigations to increase the proportion of positive cultures by reducing the time between collection and snap-freezing; in this study the interval was between 6 and 24 hrs.

The view has been expressed in several discussions that the McCoy cell system fails to yield viable isolates that can be serially passaged in the laboratory. To answer this criticism, six available isolates secured in cell culture were passaged serially six to nine times on McCoy cells. They were then passaged serially in eggs without difficulty, and have subsequently been typed by the micro-IF typing test.

An earlier study had shown that the irradiated McCoy cell culture system was superior to the yolk sac of chick embryos for primary isolation of subgroup A *Chlamydia* from genital disease, or from ocular disease associated with genital infection in London, from which the isolates have so far mainly serotyped as D, E, or F in the micro-IF test (Treharne and others, 1970). The isolates from endemic trachoma in Iran in the present study have mainly serotyped as B or C, thus resembling other isolates from endemic trachoma in the Middle East that have been typed as A, B, or C (Wang and Grayston, 1970, 1971; Treharne and others, 1971). It is clear, therefore, that the irradiated McCoy cell culture system offers a superior method of isolation for each of the two main groups of serotypes of TRIC agent, namely A, B, and C from endemic trachoma in Iran and D, E, and F from genital or ocular disease in London.

However, it is to be noted that one Iranian isolate (TRIC//IR/IOL-235/OT) from the eye of a 1-year-old girl from Dezful suffering from typical trachoma stage II (with moderate papillary hypertrophy, a number of necrotic follicles on the upper tarsal conjunctiva, and pannus) serotyped as Type D. This type has hitherto been found mainly in areas where it is postulated that TRIC agent is spread primarily by genital transmission. Hence the finding of TRIC Type D agent in a trachoma-endemic area of Iran might suggest that a low incidence of ocular infection associated with genital infection occurs in that population; or alternatively that TRIC Type D may sometimes be spread by eye to eye transmission causing endemic oriental trachoma. In this context it is of interest to note that an isolate (TRIC/WAG/MRC-1/OT) from the Gambia (Collier and Sowa, 1958) from the eye of a 10-year-old child with typical trachoma, has serotyped as Type D (Wang and Grayston, 1970, 1971; Treharne and others, 1971). On inoculation into the ophthalmic socket of a volunteer, this isolate produced a severe picture of chronic cicatricial trachoma in the conjunctiva (Collier, Duke-Elder, and Jones, 1958). In this case, although the Gambia is a trachoma endemic area, it should be noted that TRIC isolates have been secured from the genital tract of certain patients there (Sowa and others, 1965).

The present study has also confirmed the following general advantages of the McCoy cell system over the yolk sac system for the isolation of TRIC agent:

(1) A shorter time is required in which to report a clinical specimen as either positive or negative: 2 to 9 days as compared with 6 to 36 days for egg culture.

(2) The maintenance of the cell line in the laboratory avoids dependence on supplies of eggs not under laboratory control.

(3) The costs of isolation are greatly reduced.

(4) Unlike diagnosis by finding inclusions in conjunctival scrapings, the irradiated McCoy cell system secures isolates for typing and other methods of study.

It is also possible to use the cell culture technique to measure the amount of viable TRIC agent in the clinical specimen (Gordon and others, 1969; Darougar and Jones, 1971).

It is therefore concluded that an irradiated McCoy cell culture system offers a more sensitive method for the detection of *Chlamydia* in field studies of trachoma than has hitherto been available, and furthermore that this technique is truly a method of serial cultivation that yields isolates for biological characterization.

The need for a suitable source of irradiation may constitute a difficulty for some laboratories; but it has been shown that different types of ionizing irradiation, including gamma ray, *X* ray, electron beam, and beta ray, in doses ranging from 4500 to 6000 r can be successfully employed (Darougar and others, in preparation). This has led to the design of a simplified source of irradiation that will enable this procedure to be carried out in any laboratory.

Summary

The results of this study have established that isolation of TRIC agent in an irradiated McCoy cell culture system is three times as sensitive as isolation in the yolk sac of embryonated eggs when applied to endemic trachoma in Iran. This system is also at least twice as sensitive as the detection of inclusion bodies in conjunctival smears stained by iodine or Giemsa, or both. The sensitivity of the technique is achieved by the use of cells which are rendered more suitable to support the growth of TRIC agent by exposure to ionizing irradiation, and by the centrifugation of clinical specimens onto these cells. The results in this study clearly demonstrate that this technique does provide a method of serial cultivation in cell culture which yields isolates that can be transmitted in egg culture and are available for biological study.

This technique, applied to material transported on liquid nitrogen, would therefore appear to have considerable advantages for field studies of endemic trachoma. It is of interest that, although most of the isolates from endemic trachoma in Iran in this study have been serotyped as B or C, one has serotyped as D.

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Diffuse infiltrating retinoblastoma

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The term "diffuse infiltrating retinoblastoma" was introduced by Ashton (1958) to describe a form of retinoblastoma which did not produce a tumour mass within the retina. Although Manschot (1956) and Weizenblatt (1957) had described such cases previously, they did not recognize the condition as a distinct entity. Schofield (1960) described four cases of this type of retinoblastoma which presented with a hypopyon, and neoplastic cells were demonstrated in the anterior chamber paracenteses.

The purpose of the present paper is to describe a further case of this type of tumour, and to review the ten cases which have been seen in the Pathology Department of this Institute, including the four described by Schofield (1960).

Case report

CLINICAL FEATURES

A mentally defective boy aged 10 years was admitted to hospital with the history of pain in the right eye of several months' duration. There were no other complaints. Ophthalmological examination of the right eye showed a hypopyon, multiple whitish nodules on the iris, and white vitreous exudates; the left eye was normal. Radiographs of the chest showed no abnormality.

TREATMENT

Steroid therapy was begun, but glaucoma, corneal oedema, and an inferior limbal staphyloma ensued. The eye was enucleated.

PATHOLOGY

Macroscopical examination showed enlargement of the globe (antero-posterior diameter 32 mm; horizontal diameter 29 mm.). There was an inferior limbal staphyloma (Fig. 1, opposite), and exudate was present in the anterior chamber and the vitreous. The retina was diffusely thickened but there was no evidence of a tumour mass (Fig. 2, opposite). The optic disc was cupped.

Microscopical examination showed diffuse infiltration of the retina by a retinoblastoma, with no evidence of a tumour mass. The tumour was involving all the layers of the retina and was composed of cells having a little pinkish cytoplasm and hyperchromatic nuclei of varying shapes and sizes. Individual cell necrosis was seen and mitotic figures were fairly common, but there was no evidence of rosette formation (Fig. 3, opposite, and Fig. 4, overleaf).

Discrete foci of tumour cells were seen near the internal limiting membrane of the retina (Fig. 5, overleaf) and extension into the anterior vitreous had occurred, some of the cells at this site being viable but most of them being necrotic (Fig. 6, overleaf).

Posteriorly tumour cells had extended into the cupped optic disc but not into the nerve. Anteriorly extension had occurred on to the pars plana (Fig. 7) and ciliary epithelium (Fig. 8), into the iris leaf on one side, and on to both its anterior and posterior surfaces (Figs 9 and 10). Tumour cells had then extended on to the posterior surface of the cornea, the filtration angle on this side having

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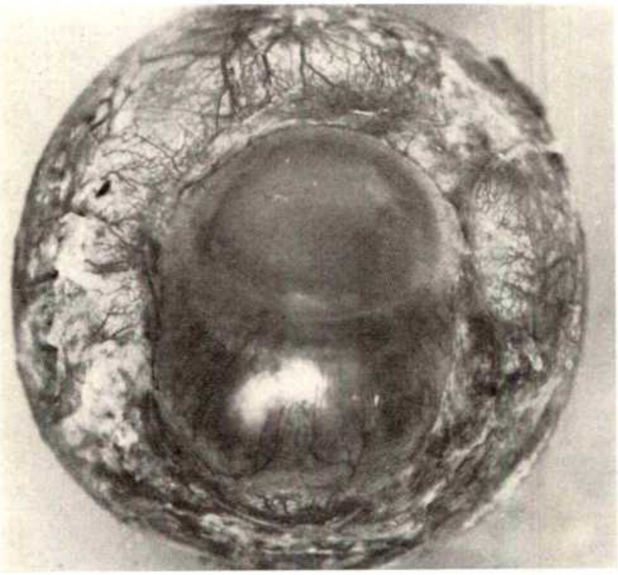

FIG. 1 *Case* 10, *showing enlarged globe with inferior limbal staphyloma and exudate within the eye*

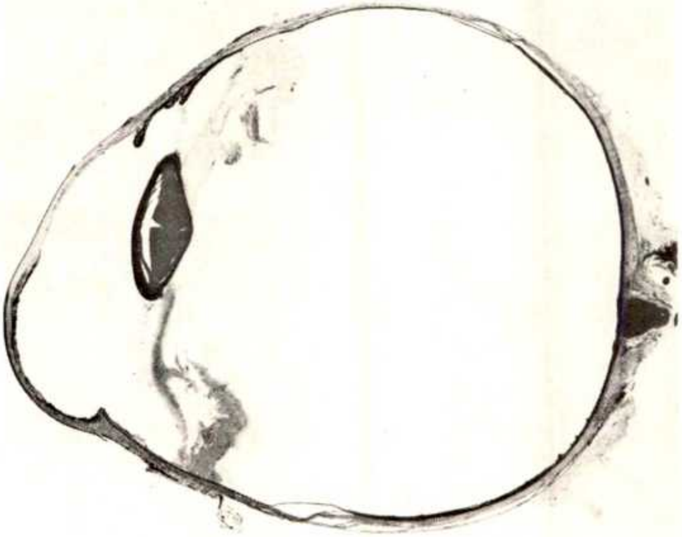

FIG. 2 *Case* 10, *showing diffuse thickening of retina, exudate in anterior vitreous, occlusion of filtration angle, and inferior staphyloma*

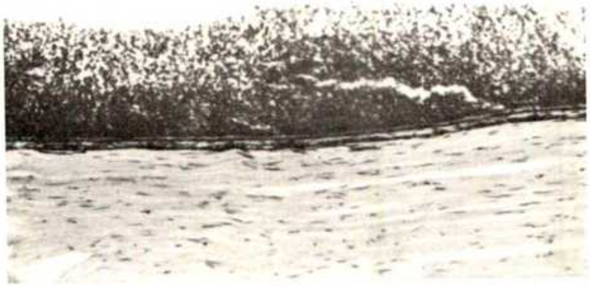

FIG. 3 *Case* 10, *showing low-power view of tumour in which cells are involving all layers of retina. Haematoxylin and eosin.* ×90

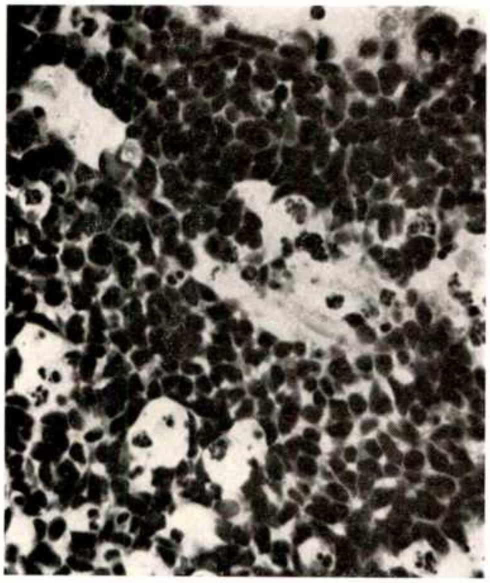

FIG. 4 *Case* 10, *showing high-power view of retinoblastoma in which cells are seen with hyperchromatic nuclei of different shapes and sizes. Several cells are undergoing necrosis but there is no evidence of any rosettes. Haematoxylin and eosin.* ×392

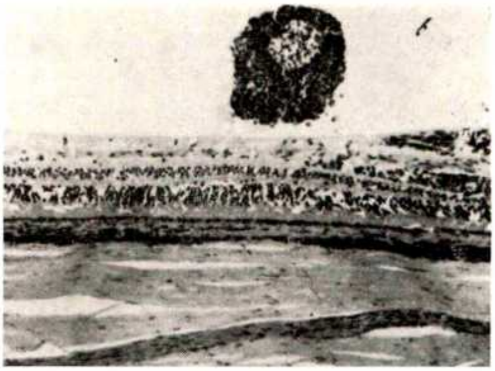

FIG. 5 *Case* 10, *showing a single focus of tumour cells lying near internal limiting membrane of retina. Haematoxylin and eosin.* ×90

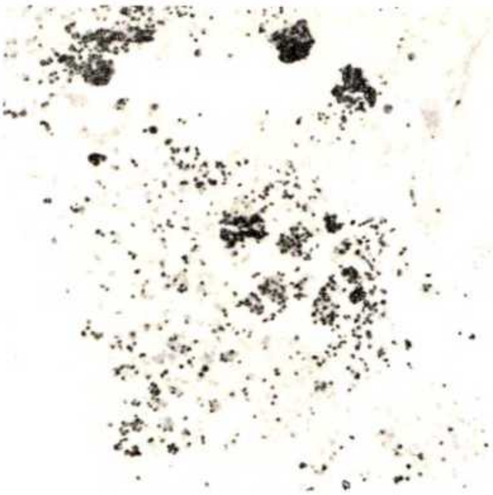

FIG. 6 *Case* 10, *showing retinoblastoma cells in vitreous. Most of the cells are necrotic. Haematoxylin and eosin.* ×90

been occluded by peripheral anterior synechiae. On the opposite side which was the inferior part of the anterior segment, most of the ciliary body and iris had been destroyed by the tumour (Fig. 11, overleaf). Near the centre of the cornea and peripherally for a short distance the markedly atrophic iris was firmly adherent to the back of the cornea, the latter showing vascularization and infiltration by neoplastic cells (Figs 12 and 13, overleaf).

Description of other cases

Ten cases of diffuse infiltrating retinoblastoma, including the case recorded in this paper, have been studied, and the findings are analysed in the Table (p. 605), which shows that in all cases the growth was entirely diffuse, there being no focal tumour mass. None of the tumours was bilateral. Seven patients were boys and three were girls. The age at onset varied between 1 year and 11 years, six of the children being more than 6 years old and the average age for the group being 6·2 years.

Six children presented with a hypopyon and anterior chamber paracentesis in four of these showed tumour cells.

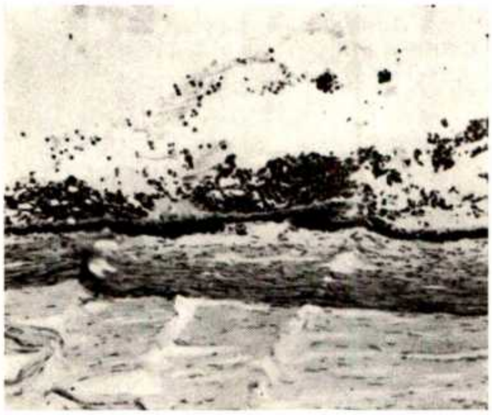

FIG. 7 *Case* 10, *showing retinoblastoma cells on pars plana. Haematoxylin and eosin.* ×90

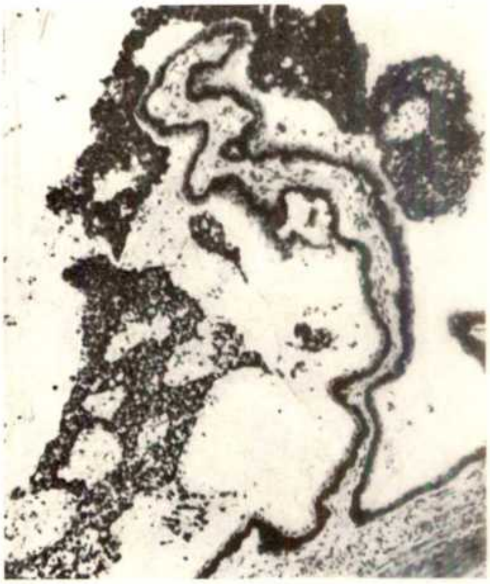

FIG. 8 *Case* 10, *showing neoplastic cells on ciliary epithelium and surrounding a ciliary process. Haematoxylin and eosin.* ×90

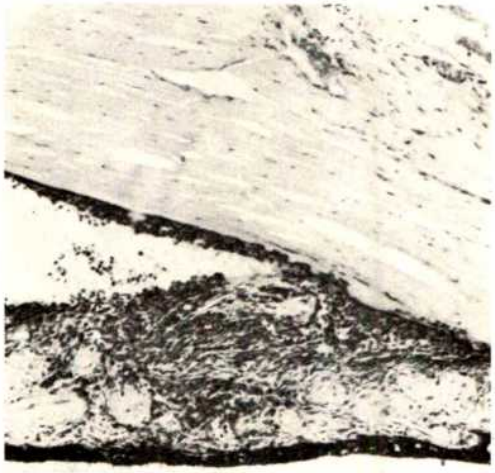

FIG. 9 *Case* 10, *showing infiltration of iris stroma by neoplastic cells which are also present on anterior iris surface and posterior corneal surface. Haematoxylin and eosin.* ×90

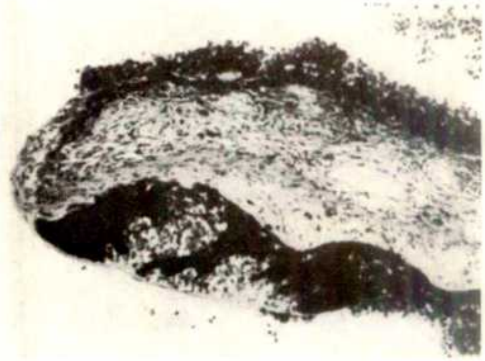

FIG. 10 *Case* 10, *showing tuuour cells on both surfaces of iris. Haematoxylin and eosin.* ×90

Histological examination of the eyes showed in every case that all layers of the retina were involved by a diffuse infiltration of closely packed cells with little cytoplasm and hyperchromatic nuclei of varying shape and size. Mitotic activity and cellular necrosis were moderate, and there was no evidence of rosette formation. Infiltration of the ciliary body, iris, and anterior chamber had occurred in eight cases, with extension into the trabecular meshwork in four of them. Neoplastic cells were seen in the vitreous in every case, in the optic nerve head in four cases, and in the optic nerve and choroid in one case.

At the present time all ten patients are alive and well, the survival times varying between 2 and 17 years (average 9·3). The apparently good prognosis is illustrated by the fact that Case 3 (Table) has survived for 14 years without recurrence or metastases despite infiltration of the trabecular meshwork by tumour cells, and that Case 7 has survived for 8 years despite invasion of the choroid.

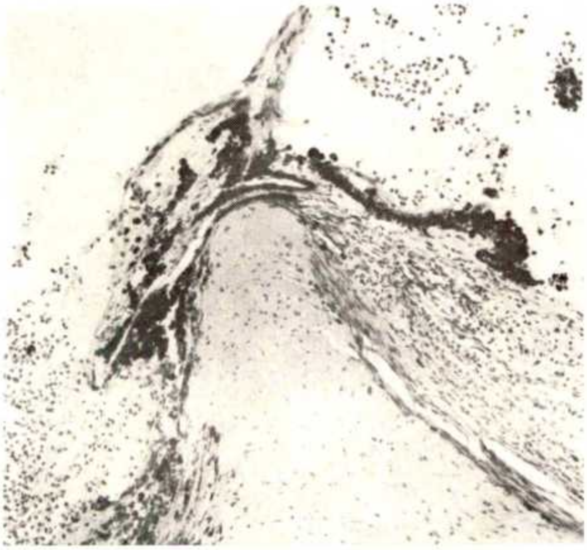

FIG. 11 *Case* 10, *showing extensive destruction of ciliary body and iris by tumour. Haematoxylin and eosin.* ×90

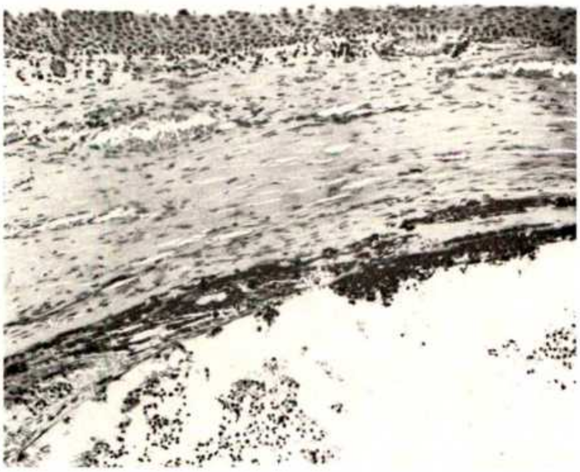

FIG. 12 *Case* 10, *showing markedly atrophic iris leaf firmly adherent to back of vascularized cornea. Haematoxylin and eosin.* ×90

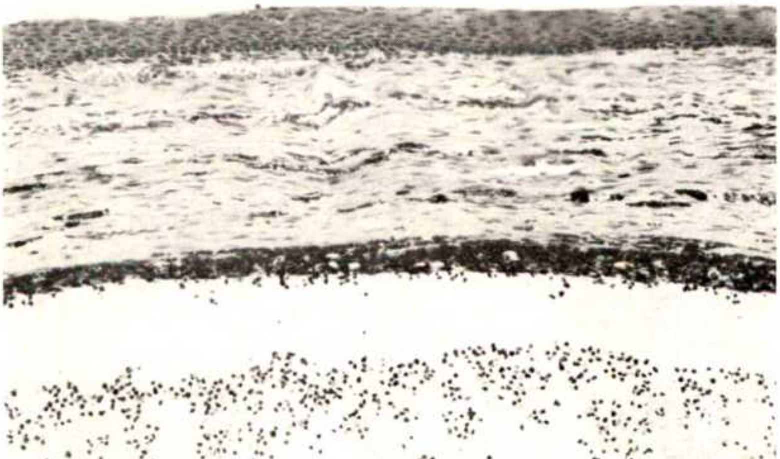

FIG. 13 *Case* 10, *showing infiltration of cornea by neoplastic cells. Haematoxylin and eosin.* ×130

Table *Summary of ten cases of diffuse infiltrating retinoblastoma*

Case no.	*Age (yrs)*	*Sex*	*Clinical features and ancillary investigations*	*Pathology*	*Treatment*	*Follow-up*
1	9½	M	4 mths' history of uveitis with hypopyon Neoplastic cells seen in anterior chamber paracentesis	Diffuse involvement of retina with no rosettes Tumour cells in ciliary body, iris, anterior chamber, and vitreous	Enucleation	Alive and well without recurrence or metastases 17 yrs after onset
2	1	M	Presented with hypopyon and buphthalmos Neoplastic cells seen in anterior chamber paracentesis	Diffuse involvement of retina with no rosettes Tumour cells in subretinal space, ciliary body, iris, vitreous, and anterior chamber	Enucleation	Alive and well without recurrence or metastases 13 yrs after onset
3	6½	M	Presented with hypopyon, subluxated cataractous lens, and raised intraocular pressure Neoplastic cells seen in anterior chamber paracentesis	Diffuse involvement of retina with no rosettes Tumour cells in vitreous, ciliary body, iris, anterior chamber, and trabecular meshwork	Enucleation	Alive and well without recurrence or metastases 14 yrs after onset
4	4¾	F	Cobalt treatment for retinoblastoma 2 yrs before onset of hypopyon and cataract Neoplastic cells seen in anterior chamber paracentesis	Diffuse involvement of retina with no rosettes Tumour cells in vitreous, ciliary body, iris, and anterior chamber Calcification of retina at site of original lesion	Enucleation	Alive and well without recurrence or metastases 14 yrs after onset
5	11	F	Hypopyon for 3 mths with raised intraocular pressure ESR, WR, and radiograph of globe normal	Diffuse involvement of retina with no rosettes Tumour cells in vitreous, ciliary body, iris, anterior chamber, trabecular meshwork, a scleral channel, subretinal space, and optic nerve head	Enucleation	Alive and well without recurrence or metastases 3 yrs after onset
6	7	M	"Peculiar-looking" eye for 3 mths in a mentally backward child Dense grey lesion almost completely covering fundus	Diffuse involvement of retina with no rosettes Tumour cells in vitreous	Enucleation	Alive and well without recurrence or metastases 10 yrs after onset
7	3	F	Mother noticed white pupil 2 yrs previously Signs of iritis and cataract on examination Chest *x* ray and ESR normal	Diffuse involvement of retina with no rosettes Tumour cells in vitreous, ciliary body, iris, anterior chamber, trabecular meshwork, optic nerve, and choroid	Enucleation	Alive and well without recurrence or metastases 8 yrs after onset
8	6	M	Treated as a case of "retinal haemangiomatosis" 10 mths previously Recently developed iris deposits and aqueous flare	Diffuse involvement of retina with no rosettes Tumour cells in vitreous, subretinal space, ciliary body, iris, anterior chamber, trabecular meshwork, and optic nerve head	Enucleation	Alive and well without recurrence or metastases 7 yrs after onset
9	3¼	M	White pupil noticed by mother for several wks	Diffuse involvement of retina with no rosettes Tumour cells in vitreous and optic nerve head	Enucleation	Alive and well without recurrence or metastases 5 yrs after onset
10	10	M	Endophthalmitis and hypopyon for 8 mths Inferior staphyloma for 1 mth with secondary glaucoma Child mentally defective	Diffuse involvement of retina with no rosettes Tumour cells in ciliary body, iris, anterior chamber, vitreous, and cupped optic disc	Enucleation	Alive and well without recurrence or metastases 2 yrs after onset

ESR = erythrocyte sedimentation rate
WR = Wassermann reaction

Discussion

Of 720 cases of retinoblastoma examined histologically in the Department of Pathology of this Institute between the years 1949 and 1970, only ten (1·4 per cent.) have been diagnosed as diffuse, infiltrating tumours. Several interesting features have emerged from the study of these ten cases. The average age of the patients is higher than that of the usual type of retinoblastoma which presents with a tumour mass, and none of these tumours was bilateral. Patients frequently present with a hypopyon so that examination of an anterior chamber paracentesis for neoplastic cells is an important diagnostic procedure. Rosettes are not a feature of this tumour, and as far as this small series of cases is concerned the tumours have a good prognosis.

The tumour originates either as a simple diffuse growth or as multiple foci of growth which coalesce. Spread may then occur through the ciliary body and iris and extend into the anterior chamber, and may in some cases invade the trabecular meshwork. Tumour cells may grow into the vitreous or upon the pars plana and ciliary processes. Invasion of the choroid or optic nerve occurs in some cases.

In seven of the ten cases presenting with this tumour, the age of the patient was 4¾ years or over, suggesting that the neoplasms arise at a later age than the usual type of tumour. In three of the cases, however, the age at onset was 1 year (Case 2), 1 year (Case 7), and 3 years (Case 9) respectively, which shows that the tumour can arise at an earlier age and that some (Cases 2 and 9) may grow more rapidly than others, although there were no histological features to account for this. On the whole, however, the rate of growth is slow, as illustrated by Case 4 in which the original lesion was treated by cobalt irradiation 2 years before the onset of a hypopyon, and by Case 7 in which the mother noticed a white pupil 2 years before bringing the child to hospital. A rapidly-growing tumour would be expected to produce an expanding growth within the area of the retina while a slowly-growing tumour would be more likely to spread through the retina. There seems to be little doubt that the tumour must have a low malignant potential which would explain the apparently favourable prognosis of this uncommon neoplasm, for in spite of invasion of the trabecular meshwork in four cases (Cases 3, 5, 7, and 8) and of the choroid in one (Case 7), the patients have survived with no evidence of recurrence or metastases for periods varying between 3 and 14 years after enucleation. The question whether or not the low malignant potential is due to the tumours' origin from more highly differentiated tissue is not clear, because the rosettes seen in the better differentiated retinoblastomas were not observed in the ten cases of this series. It is possible, however, that they were absent because the tumour did not produce a mass, and there was insufficient space within the retina for their development.

Summary

Ten cases have been described of a type of retinoblastoma which is both diffuse and infiltrating, and which does not form a tumour mass; four of these cases have been reported previously (Schofield, 1960). The average age of the patients is higher than that found in the usual type of retinoblastoma, and the majority present for the first time with a hypopyon. Bilaterality was not a feature, and rosette formation was not seen. The prognosis after enucleation appears to be good.

I am most grateful to Prof. Norman Ashton for his advice during the preparation of this paper.

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Relationships between ocular dimensions and the effects of provocative tests

Water drinking

Homatropine eye drops

Water drinking and homatropine eye drops

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Weekers, Lavergne, and Prijot (1958), Davenport (1959), and Perkins and Jay (1960) have all commented on a high incidence of myopia in open-angle glaucoma.

Abdalla and Hamdi (1970) showed that myopic eyes have higher ocular tensions than emmetropic eyes in most age groups. The findings of Tomlinson and Phillips (1970) agreed with this, but showed that ocular tension correlated more closely with the axial length of the eye (*i.e.* high axial length was associated with higher ocular tension than low axial length) than with the refraction.

Tomlinson and Phillips (1969) have reported a correlation between high cup-to-disc area ratio and high axial length of the eye. Armaly (1969) has suggested that the cup/disc ratio may be a factor determining the susceptibility of eyes with high intraocular pressure to visual field defects. A tendency to high ocular tension and large cup/disc ratio in eyes of long axial length may partly explain the high prevalence of open-angle glaucoma in myopic eyes.

A very clear association between shallowness of the anterior chamber and closed-angle glaucoma is known (Rosengren, 1931; Törnquist, 1956; Lowe, 1969). In open-angle glaucoma also, a shallower than normal anterior chamber has been observed (Rosengren, 1931; Törnquist and Brodén, 1958; Tomlinson and Leighton, in preparation, *i.e.* unpublished data).

Object of present investigation

To find out whether the effects of provocative agents used in the diagnosis of open-angle glaucoma were influenced by dimensions of the eyeball.

Methods

PROVOCATIVE TESTS

38 subjects had 96 provocative tests of four different types: Table I (overleaf) gives the number of provocative tests and the types of subjects who had them.

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Table I *Particulars of 38 subjects tested, showing numbers of tests given to each category of patient*

Provocative tests done	*Open-angle glaucoma*		*Low tension glaucoma cases*	*Relatives of open-angle glaucoma patients*	*Normal subjects*	*Total*	
	Suspects	*Cases*				*Patients*	*Tests*
a, b, c	18	1	1	0	0	20	60
c, d	12	0	1	4	1	18	36
a, b, c, d	30	1	2	4	1	38	96

(*a*) water-drinking tonography test

(*b*) homatropine tonography test

(*c*) water-drinking homatropine tonography test

(*d*) water-drinking homatropine applanation test

(1) Twenty subjects had three outflow tests:

(*a*) a water-drinking tonography test

(*b*) a homatropine tonography test

(*c*) a water-drinking homatropine tonography test (Leighton, Phillips, and Gibbs, 1970).

In these tests, the effects on aqueous outflow and applanation tension of water drinking (20 ml./kg. body weight) and/or gutt. homatropine 2 per cent. in randomized order were estimated from the differences between tonographic and tonometric readings immediately before and 45 minutes after provocation.

(2) Eighteen other subjects had two tests:

(*c*) a water-drinking homatropine tonography test as above

(*d*) a water-drinking homatropine applanation test (Leighton and Phillips, 1971).

The effect of the provocation (*d*) was measured from the difference between applanation tensions taken immediately before and 45 minutes after provocation.

OCULAR RIGIDITY

This was measured from Friedenwald's Nomogram (1955 calibration) by applanation and 5·5 g. Schiötz readings in sixty subjects. These comprised the 38 patients shown in Table I with the addition of 22 patients who did not have the provocative tests:

Open-angle glaucoma suspects	4	22
Cases of open-angle glaucoma	1	
Cases of low tension glaucoma	1	
Relatives of open-angle glaucoma patients	2	
Relatives of closed-angle glaucoma patients	14*	

OCULAR DIMENSIONS

The following were measured in the 38 subjects from the eye which received the provocative tests, and from one eye of each of the 22 additional subjects mentioned above:

(*i*)	Corneal diameter	from a colour photograph of the anterior surface of the eye
(*ii*)	Corneal thickness	by the No. I attachment for the Haag-Streit 900 slit lamp
(*iii*)	Central corneal radius	by the Zeiss keratometer
(*iv*)	Corneal astigmatism	
(*v*)	Anterior chamber depth	by the No. II attachment for the Haag-Streit 900 slit lamp
(*vi*)	Lens thickness	from an antero-posterior axis trace of the eye obtained by A-scan ultrasonography
(*vii*)	Length of vitreous body	
(*viii*)	Axial length of the eyeball	from the addition of (*v*), (*vi*), and (*vii*)

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* Relatives of closed-angle glaucoma patients were used in this part of the survey to extend the range of ocular dimensions measured

None of the patients was having treatment for glaucoma at the time that the above dimensions were taken. If treatment with gutt. pilocarpine had been started beforehand this was discontinued 48hrs before the measurements were made. Wilkie, Drance, and Schulzer (1969) demonstrated reduction in anterior chamber depth in patients on miotic eye drops.

Results and discussion

OCULAR DIMENSIONS AND PROVOCATION

Correlation coefficients (r_s) are recorded in Tables II and III for twenty patients who had three outflow tests, and in Table IV for eighteen patients who had an outflow test and an applanation test. The Spearman rank correlation method (Siegel, 1956) was used. Analysis of the ages of the subjects and correlations of these with lens thickness and corneal astigmatism are given in Table V.

THREE PROVOCATIVE TESTS IN EACH OF TWENTY SUBJECTS

The rise in applanation tension found in the three outflow tests 45 minutes after provocation would have been affected by the fall in ocular tension due to the initial tonography which had been done after the initial applanation tension and before provocation.

No significant correlations were found between ocular dimensions and rise in Po/C in any of the three provocative outflow tests on twenty patients.

Test (*a*) *Water-drinking tonography test*

No significant correlations between the dimensions and rise in outflow resistance were found. The small non-significant rise in outflow resistance which occurred might have explained this. However, the rise in applanation tension correlated significantly with corneal diameter, length of vitreous body, and lens thickness (see Table II)—$0{\cdot}01 < P < 0{\cdot}05$ in each case. Thus water loading induced a greater rise in ocular tension in eyes with small corneal diameters than in those with large diameters. Presumably such eyes have only a small circumference of filtration angle and perhaps also small total amount of trabecular meshwork, which is less able to allow the passage of the extra aqueous formed after water drinking.

The correlation between the rise in applanation tension and the length of the vitreous body suggests that water loading becomes less effective as a provocative agent in large eyes. A small rise in applanation tension tended to be associated with large axial length but this trend did not reach significance.

It is difficult to understand why variation in lens thickness correlated directly with rise in applanation tension due to water drinking. The explanation was presumably an indirect one. The rise in applanation tension after water was age-dependent (Armaly, 1970, has also shown this) as was lens thickness, ($r_s = +0{\cdot}471$; $+0{\cdot}384$ respectively; $0{\cdot}01 < P < 0{\cdot}05$ in each case) so the significant correlation between lens thickness and rise in applanation tension presumably reflected the age-dependence of each. A significant inverse correlation between lens thickness and anterior chamber depth was found ($r_s = -0{\cdot}440$; $0{\cdot}01 < P < 0{\cdot}05$). Shallowness of the anterior chamber, which François, Rabaey, Neetens, and Evens (1958) have shown experimentally to be associated with a high outflow resistance, tended to be associated with a high rise in applanation tension ($r_s = -0{\cdot}103$; $P > 0{\cdot}05$) though not significantly so. The expected association of a shallow anterior chamber in an eye with a thick lens might therefore have contributed to the rise in applanation tension found, and thus to the correlation between lens thickness and effect on applanation tension of the water drinking.

The effect of water drinking on outflow resistance was slight compared with its effect on applanation tension (Tables II and III). Accordingly, the rise in applanation tension found was probably related more to an increase in aqueous production than to an increase in outflow resistance. The higher rise in applanation tension after water drinking found in older subjects could have been due to various factors, including greater haemodilution after easier absorption from the gut, less effective diuresis because of poorer renal function, or to an easier passage of water across the blood–aqueous barrier.

Table II *Twenty subjects. Correlations between* (1) *Effects on applanation tension of water drinking and/or gutt. homatropine and* (2) *Ocular dimensions and age*

Tonography test	*Rise in applanation tension*		*Correlation coefficients (r_s) between rise in applanation tension and:*							
	Mean	*SD*	*Corneal diameter*	*Horizontal corneal radius*	*Corneal astigmatism (corneal radii: horizontal minus vertical)*	*Anterior chamber depth*	*Lens thickness*	*Length of vitreous body*	*Axial length of eyeball*	*Age*
(*a*) Water-drinking	+3·05	2·68	−0·399	+0·043	−0·230	−0·103	+0·427	−0·420	−0·248	+0·471
	S		S*	NS	NS	NS	S*	S*	NS	S*
(*b*) Gutt. homatropine	+0·55	2·04	−0·518	+0·276	−0·027	−0·237	+0·046	−0·283	−0·361	+0·273
	NS		S*	NS	NS	NS	NS	NS	NS	NS
(*c*) Water-drinking and gutt. homatropine	+5·25	5·16	−0·182	−0·105	−0·338	−0·014	−0·049	−0·557	−0·451	+0·308
	S		NS	NS	NS	NS	NS	*S*	S*	NS

S = Significant at P < 0·01
S* = Significant at 0·01 < P < 0·05
NS = Not significant P > 0·05
SD = Standard deviation

Correlation coefficients for $\left.\begin{matrix} P = 0{\cdot}05 \\ P = 0{\cdot}01 \end{matrix}\right\}$ are $\left\{\begin{matrix} 0{\cdot}377 \\ 0{\cdot}534 \end{matrix}\right.$

The rise in applanation tension quoted is the difference between an initial applanation reading taken just before a 4-minute tonography before provocation, and a second applanation reading 45 minutes after provocation

Table III *Twenty subjects. Correlations between* (1) *Effects on outflow resistance of water drinking and/or gutt. homatropine and* (2) *Ocular dimensions and age*

Tonography test	*Rise in outflow resistance*		*Correlation coefficients (r_s) between rise in outflow resistance and:*							
	Mean	*SD*	*Corneal diameter*	*Horizontal corneal radius*	*Corneal astigmatism (corneal radii: horizontal minus vertical)*	*Anterior chamber depth*	*Lens thickness*	*Length of vitreous body*	*Axial length of eyeball*	*Age*
(*a*) Water-drinking	+3·28	8·45	−0·127	−0·117	−0·008	+0·164	—0·150	−0·130	−0·043	+0·148
	NS		NS	NS	NS	NS	NS	NS	NS	NS
(*b*) Gutt. homatropine	+5·20	10·86	−0·447	+0·114	+0·279	−0·268	−0·012	−0·271	−0·265	−0·241
	S		S*	NS	NS	NS	NS	NS	NS	NS
(*c*) Water-drinking and gutt. homatropine	+5·73	9 68	−0 050	+0·110	−0·190	−0·125	+0·149	+0·189	+0·178	+0·089
	S		NS	NS	NS	NS	NS	NS	NS	NS

S = Significant at P < 0·01
S* = Significant at 0·01 < P < 0·05
NS = Not significant P > 0·05
SD = Standard deviation

Correlation coefficients for $\left.\begin{matrix} P = 0{\cdot}05 \\ P = 0{\cdot}01 \end{matrix}\right\}$ are $\left\{\begin{matrix} 0{\cdot}377 \\ 0{\cdot}534 \end{matrix}\right.$

The rise in outflow resistance quoted is obtained from the difference between an initial 4 minute tonography before provocation, and one done 45 minutes after provocation

Test (b) Homatropine tonography test

Significant correlations were found between corneal diameter and both rise in outflow resistance and rise in applanation tension (Fig. 1) (0·01<P<0·05 in each case). Relaxation of tonus in the ciliary body after instillation of gutt. homatropine in an eye with a small corneal diameter therefore resulted in a greater rise in outflow resistance and applanation tension than it did in an eye with a large corneal diameter, perhaps because of the small circumference of filtration angle and hence a relatively small amount of trabecular meshwork in eyes with small corneal diameters.

Bárány and Christensen (1967) demonstrated a greater increase in outflow resistance after gutt. homatropine 5 per cent. in (open-angle) glaucomatous eyes than in normal eyes. This difference in effect might, in part, have been due to variation in corneal size, although a small cornea is not a conspicuous feature of eyes with open-angle glaucoma.

Test (*c*) *Water-drinking homatropine tonography test*

The rise in applanation tension in this tonography test correlated inversely with both length of the vitreous body and axial length of the eyeball ($P<0{\cdot}01$ and $0{\cdot}01<P<0{\cdot}05$ respectively). The effect of the provocation was therefore significantly less in large than in small eyeballs. No significant correlations between the ocular dimensions and rise in outflow resistance were found.

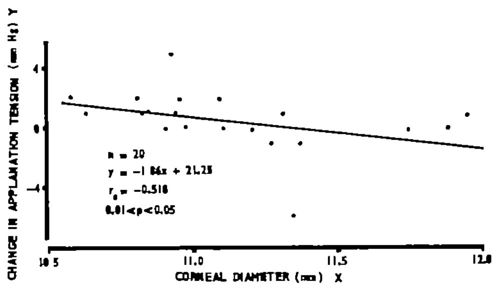

FIG. 1 *Change in applanation tension and corneal diameter in homatropine tonography test. Corneal diameter also correlated significantly with rise in outflow resistance* ($r_s = -0{\cdot}477$; $0{\cdot}01<P<0{\cdot}05$)

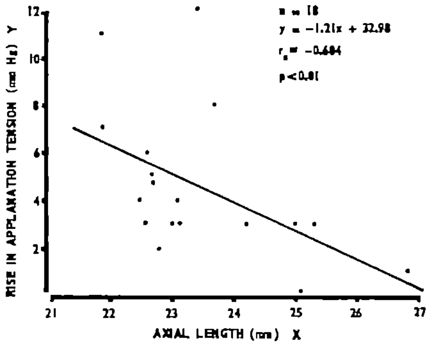

FIG. 2 *Rise in applanation tension and axial length of eyeball in a water-drinking homatropine tonography test*

TWO PROVOCATIVE TESTS IN EACH OF EIGHTEEN SUBJECTS

Correlations between ocular dimensions and the effects of these provocative tests on applanation tension and outflow resistance are recorded in Table IV (overleaf).

Test (*c*) *continued Water-drinking homatropine tonography test*

Significant correlations were found between the rise in applanation tension and both the depth of the anterior chamber and the axial length of the eyeball (Fig. 2) ($r_s = -0{\cdot}632$ and $-0{\cdot}604$ respectively; $P<0{\cdot}01$ in each case). Eyes with shallow anterior chambers and short axial lengths therefore showed a greater rise in applanation tension after the provocation than eyes with deep anterior chambers and large axial lengths. The same trends were found between rise in Po/C, and both depth of anterior chamber ($r_s = -0{\cdot}461$; $0{\cdot}01<P<0{\cdot}05$) and axial length of eyeball ($r_s = -0{\cdot}395$; $P>0{\cdot}05$; the correlation coefficient for $P = 0{\cdot}05$ is $0{\cdot}399$).

When this same test was done on twenty patients (see paragraph (*c*) above), no correlation between rise in applanation tension and anterior chamber depth was found ($r_s = -0{\cdot}014$; $P<0{\cdot}05$). The reason for the wide discrepancy between the samples of twenty and eighteen subjects in the correlations of anterior chamber depth with rise in

Table IV *Eighteen subjects. Correlations between* (1) *Effects on outflow resistance and applanation tension of water drinking and gutt. homatropine and* (2) *Ocular dimensions and age*

Test	*Rise in*				*Correlation coefficients* (r_s) *between rise in applanation tension or outflow resistance and:*							
	Applanation tension		*Outflow resistance*		*Corneal diameter*	*Horizontal corneal radius*	*Corneal astigmatism (corneal radii: horizontal vertical)*	*Anterior chamber depth*	*Lens thickness*	*Length of vitreous body*	*Axial length of eyeball*	*Age*
	Mean	*SD*	*Mean*	*SD*								
(*c*) (i) Water-drinking homatropine tonography			+8·30	10·88	−0·088	−0·190	−0·084	−0·112	+0·503	−0·296	−0·250	+0·309
			S		NS	NS	NS	NS	S*	NS	NS	NS
(ii) Water-drinking homatropine tonography	+4·61	3·18			−0·111	+0·273	−0·490	−0·632	+0·278	−0·354	−0·604	+0·040
	S				NS	NS	S*	*S*	NS	NS	*S*	NS
(*d*) Water-drinking homatropine applanation	+5·17	3·58			−0·369	+0·150	−0·482	−0·150	−0·232	−0·031	−0·232	−0·276
	S				NS	NS	S*	NS	NS	NS	NS	NS

S = Significant at $P < 0·01$
S* = Significant at $0·01 < P < 0·05$
NS = Not significant $P > 0·05$
SD = Standard deviation

Correlation coefficients for $\left.\begin{array}{l} P = 0·05 \\ P = 0·01 \end{array}\right\}$ are $\left\{\begin{array}{l} 0·399 \\ 0·564 \end{array}\right.$

The rise in outflow resistance in (c) (i) and rise in applanation tension in (c) (ii) above are the differences between tonographic and tonometric readings taken immediately before, and 45 minutes after provocation. (c) (i) and (c) (ii) relate to the same visit. The rise in applanation tension in (d) is the difference between applanation tension taken immediately before and 45 minutes after provocation applanation tension is probably as follows. In the eighteen subjects, in whom both shallow anterior chamber and short axial length correlated with a high rise in applanation tension, a correlation between shallow anterior chamber and short axial length almost reached significance ($r_s = +0{\cdot}375$; $P > 0{\cdot}05$; r_s for $P = 0{\cdot}05$, the borderline of significance, is $0{\cdot}399$). An explanation for a high rise in applanation tension could therefore have been either a shallow anterior chamber or short axial length, or both. In the twenty subjects short axial length correlated with a high rise in applanation tension, but very little correlation between axial length and anterior chamber depth was found ($r_s = +0{\cdot}152$; $P > 0{\cdot}05$). This probably explains the absence of correlation between anterior chamber depth and rise in applanation tension in the twenty subjects and may well indicate that in the eighteen subjects short axial length was more important than a shallow anterior chamber in producing a high rise in applanation tension.

A greater rise in applanation tension tended to be found in eyes with small corneal diameter, but this trend did not approach significance ($r_s = -0{\cdot}111$; $P > 0{\cdot}05$). However, as shallow anterior chamber was associated with small corneal diameter ($r_s = +0{\cdot}519$; $0{\cdot}01 < P < 0{\cdot}05$), the latter could also have contributed to the correlation found between shallow anterior chamber and a high rise in applanation tension after provocation.

A significantly greater rise in applanation tension was found in eyes with a larger horizontal than vertical corneal radius (*i.e.* "with-the-rule" astigmatism) than in those with a greater vertical than horizontal corneal radius (*i.e.* "against-the-rule" astigmatism) ($r_s = -0{\cdot}490$; $0{\cdot}01 < P < 0{\cdot}05$).

Rise in outflow resistance correlated significantly with lens thickness ($r_s = +0{\cdot}503$; $0{\cdot}01 < P < 0{\cdot}05$) as it had done with the rise in applanation tension in test (*a*), the water-drinking tonography test.

Test (*d*) *Water-drinking homatropine applanation test*

The only significant correlation here was between corneal astigmatism and rise in applanation tension ($r_s + -0{\cdot}482$; $0{\cdot}01 < P < 0{\cdot}05$) (Fig. 3). This result agreed very closely with that for the water-drinking homatropine tonography test (see (*c*) continued above and Table IV) in these same eighteen individuals. Marin-Amat (1956) has shown that corneal astigmatism "against-the-rule", *i.e.* greater vertical than horizontal corneal radius, increases with age. This trend was not significant in these eighteen individuals ($r_s = +0{\cdot}120$; $P > 0{\cdot}05$). It seems surprising that the rise in applanation tension became

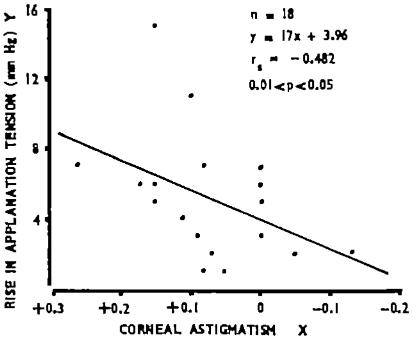

FIG. 3 *Rise in applanation tension and corneal astigmatism in a water-drinking homatropine applanation test*

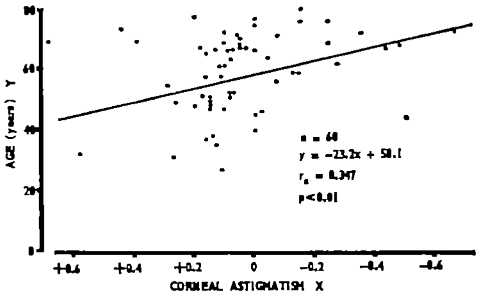

FIG. 4 *Age related to corneal astigmatism*

progressively less with increasing "against-the-rule" corneal astigmatism, which tended, though not significantly, to correlate with increasing age.

In the two other samples, *i.e.* twenty subjects who had three outflow tests, and sixty subjects in whom ocular rigidity was measured (see Fig. 4 and Table V), the correlations between increasing age and increasing "against-the-rule" astigmatism were both significant.

Table V *Age, lens thickness, and corneal astigmatism of subjects and correlations between these*

Sample comprised subjects who had	*Number of subjects*	*Lens thickness*		*Correlation coefficient* (r_s) *(Lens thickness/age)*	*Age (yrs)*		*Correlation coefficient* (r_s) *(Corneal astigmatism/age)*	*Corneal astigmatism (corneal radii: horizontal minus vertical)*		*Correlation coefficients* (r_s) *for*	
		Mean	*SD*		*Mean*	*SD*		*Mean*	*SD*	$P=0·05$	$P=0·01$
(*a*), (*b*), (*c*)	20	4·72	0·43	+0·384 S*	65·8	9·4	+0·396 S*	+0·054	0·232	0·377	0·534
(*c*), (*d*)	18	4·68	0·44	+0·642 *S*	55·4	11·2	+0·120 NS	+0·071	0·157	0·399	0·564
Ocular rigidity	60	4·71	0·41	+0·465 **S*	59·1	13·1	+0·347 *S*	+0·044	0·193	0·255	0·330

(*a*) Water-drinking tonography
(*b*) Homatropine tonography
(*c*) Water-drinking homatropine tonography
(*d*) Water-drinking homatropine applanation

SD = Standard deviation
NS = Not significant
S* = $0·01 < P < 0·05$
S = $P < 0·01$
**S* = $P < 0·001$

OCULAR RIGIDITY AND OCULAR DIMENSIONS

Ocular rigidity and axial length

These correlated significantly ($r_s = -0·322$; $N = 60$; $P<0·02$) (Fig. 5), *i.e.* large eyes had low ocular rigidity.

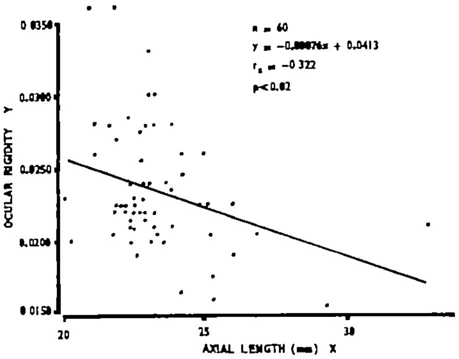

FIG. 5 *Ocular rigidity related to axial length of eyeball*

Ytteborg (1960), in experiments on enucleated eyes, noted that ocular rigidity was less in large than in small eyes. Phillips and Quick (1960) and Phillips and Shaw (1970) have shown experimentally that, in impression tonometry on hollow rubber spheres simulating eyeballs, volumes of indentation are dependent on total volume. Luyckx (1967) found, by applanation and 10 g. Schiötz tonometry *in vivo* in seventy subjects, that ocular rigidity was inversely proportional to the square of the axial length. It follows, therefore, that an impression tonometer would sink more easily into a large myopic or buphthalmic eye than into a small eye.

Ocular rigidity as measured here represents a discrepancy between the estimated intraocular pressure measured by applanation and Schiötz tonometry. Factors other than ocular volume determine ocular rigidity. It is known that corneal radius can affect Schiötz tonometer readings (Friedenwald, 1954) but that the effect of varying corneal radius on applanation tonometer readings is negligible (Schmidt, 1956). As no correlation between ocular rigidity and corneal radius was found, variation in the latter does not appear to have affected readings with the Schiötz tonometer compared with applanation readings.

Ocular rigidity and lens thickness

A significant correlation was found between these measurements ($r_s = -0{\cdot}268$; $N = 60$; $0{\cdot}01 < P < 0{\cdot}05$), in that eyes with thicker lenses showed lower ocular rigidities.

As eyes with longer axial lengths usually contain thinner lenses (see Lowe, 1970), a positive correlation between lens thickness and ocular rigidity might have been expected. But as no correlation between lens thickness and axial length was found for this sample ($r_s = -0{\cdot}056$; $N = 60$; $P > 0{\cdot}50$), no inconsistency exists.

Weale (1963) mentioned conflicting reports from various authors on change in ocular rigidity with increasing age, some reporting a fall in ocular rigidity and others an increase. In our sixty subjects, although lens thickness was age-dependent (Table V) ($r_s = +0{\cdot}465$; $P > 0{\cdot}001$), ocular rigidity was not ($r_s = 0{\cdot}149$; $P > 0{\cdot}05$). The correlation found between lens thickness and ocular rigidity could not therefore be explained in terms of their age dependence.

Conclusions

EYEBALL SIZE AND EFFECTS OF PROVOCATION

Significant correlations were found in outflow tests between a high rise in applanation tension and short length of vitreous body when water was used alone, and between a high rise in applanation tension and short lengths of both vitreous body and eyeball when water was combined with gutt. homatropine (Tables III and IV; Fig. 3). A tendency for small eyeballs to respond to water and homatropine by a high rise in Po/C very nearly reached significance ($r_s = -0{\cdot}395$; $P > p{\cdot}05$; correlation coefficient for $P = 0{\cdot}05$ is $0{\cdot}399$). This dependence of test effect on eyeball size was not significant in the water-drinking homatropine applanation test, although the correlation approached significance (Table IV). Presumably the dependence of rise in applanation tension on eyeball size in an outflow test was partly due to the fall in ocular tension after the initial tonography, carried out after the first applanation reading but before water or water and homatropine were given. No significant correlation was found between the initial applanation tension and anterior chamber depth or axial length of eyeball, nor between these last two dimensions and the initial outflow resistance. The relatively small test effect in large eyes probably adversely affects the ability of water-drinking and gutt. homatropine to discriminate between glaucoma and normality in such eyes, as large eyeballs are probably more susceptible to open-angle glaucoma than small eyes.

CORNEAL DIAMETER AND ANTERIOR CHAMBER DEPTH

Water drinking or homatropine, each given separately, induced a rise in applanation tension which was greater in eyes with a small corneal diameter than in those with a large diameter. Homatropine alone induced a greater rise in outflow resistance in eyes with small than in those with large corneal diameters.

It is unlikely that correlation of the response to provocation and corneal diameter increases the ability of the provocative agents to differentiate between glaucoma and normality.

The greater effect of water drinking combined with gutt. homatropine on applanation tension found in eyes with shallow anterior chambers in the eighteen subjects (but not in the twenty subjects) might have been regarded as a useful trend because, as has been mentioned above, patients with open-angle glaucoma tend to have shallow anterior chambers. However, unfortunately for this test, the trend probably resulted from a tendency to a high rise in applanation tension in eyes of short axial length, because a fairly close correlation was found between anterior chamber depth and axial length in the eighteen subjects but not in the twenty subjects.

CORNEAL ASTIGMATISM AND EFFECTS OF PROVOCATION

The well-known change from "with-the-rule" to "against-the-rule" refractive astigmatism with increasing age is probably chiefly due to a change in corneal astigmatism. McLenachan and Loran (1967) have shown that "against-the-rule" refractive astigmatism is commoner in patients with closed-angle glaucoma than in normal subjects. They attributed the greater likelihood of angle closure in "against-the-rule" astigmatism to a greater vertical than horizontal corneal radius. Surprisingly, the greater rise in applanation tension after water drinking combined with homatropine was found in "with-the-rule" corneal astigmatism (Fig. 3). This is the reverse of the trend with increasing age, and the trend in closed-angle glaucoma. It is unlikely that a greater horizontal than vertical corneal radius is a feature of eyes with open-angle glaucoma and its correlation with rise in applanation tension may reveal an unreliable feature of the test. It is very difficult to explain this trend.

Full evaluation of the factors which determine effects of provocation would require more measurements, both ocular and extraocular. Analysis of these data as well as those already considered here would become more complex. The rôle of these dimensions in determining the response to provocation would be uncertain because of the many possible relationships between the dimensions and the effects of provocation, and between the dimensions themselves. The connection between the cause, *i.e.* provocation, and effect of the provocation, therefore becomes increasingly obscure as more dimensions are considered.

Ocular dimensions, such as corneal astigmatism and corneal diameter, which appear to determine the effects of the provocation, seem to have no relevance to open-angle glaucoma, and may explain some unsatisfactory results of provocative tests.

The smaller effect of provocation in eyes of great axial length (or surface area of corneoscleral envelope: Phillips and Shaw, 1970) is probably a factor which adversely affects the ability of a test to discriminate between glaucoma and normality, and may well account for some false negative results of provocative tests in patients with open-angle glaucoma and high myopia.

Summary

Twenty subjects (eighteen open-angle glaucoma suspects and two cases of definite open-angle glaucoma) had three outflow tests: (a) water-drinking tonography test, (*b*) a homatropine 2 per cent. tonography test, and (*c*) a water-drinking homatropine 2 per cent. tonography test. A dose of 20 ml./kg. body weight of water was given.

The following significant correlations ($P<0{\cdot}05$) were found between ocular dimensions and rise in applanation tensions and rise in outflow resistance in these three outflow tests:

Test (a) Water-drinking tonography test

A high rise in applanation tension was associated with:

(*i*) Small corneal diameter,

(*v*) A thick lens,

(*vii*) Short length of vitreous body and greater age.

Test (b) Homatropine tonography test

A high rise in applanation tension and outflow resistance was associated with:

(*i*) Small corneal diameter

Test (c) Water-drinking homatropine tonography test

A high rise in applanation tension was associated with:

(*vii*) Short length of vitreous body,

(*viii*) Short axial length of eyeball.

Eighteen subjects (twelve open-angle glaucoma suspects, one case of definite open-angle glaucoma, four relatives of patients with open-angle glaucoma, and one normal subject) had two tests in which water-drinking and gutt. homatropine were given:

(*c*) an outflow test (*i.e.* same as (*c*) above),

and

(*d*) a tonometry (only) test.

The following significant ($P<0{\cdot}05$) correlations were found:

Test (c) Water-drinking homatropine tonography test

A high rise in applanation tension was associated with:

(*iv*) "With-the-rule" corneal astigmatism,

(*v*) Shallowness of anterior chamber,

(*viii*) Short axial length of eyeball.

A high rise in Po/C was associated with:

(*v*) Shallowness of anterior chamber

A high rise in outflow resistance was associated with:

(*vi*) A thick lens

Test (d) Water-drinking homatropine applanation test

A high rise in applanation tension was associated with:

(*iv*) "With-the-rule" corneal astigmatism

In the sample of eighteen subjects, eyeballs with shallow anterior chambers tended to have short axial lengths. The rise in applanation tension found was probably due to a short axial length rather than to a shallow anterior chamber.

Variations in the axial length of the eyeball and the length of the vitreous, which tend to correlate inversely with the effect of the provocation used, are likely to cause a *reduction* in the ability of the provocative agents used to discriminate between open-angle glaucoma and normality.

In sixty subjects, a significant association between increasing age and a change from "with-the-rule" to "against-the-rule" corneal astigmatism was found.

In the same sixty subjects, a significant tendency for low ocular rigidity to be associated with a high axial length of the eyeball was found, suggesting that Schiötz tonometry gives an erroneously low estimate of intraocular pressure on larger than "normal" eyes and an erroneously high reading in smaller than "normal" eyes.

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Provocative test combining water drinking and homatropine eye drops

Applanation *versus* tonography

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In a previous study (Leighton, Phillips, and Gibbs, 1970), a provocative outflow test using a combination of water drinking (20 ml./kg. body weight) and gutt. homatropine 2 per cent. in 24 open-angle glaucoma suspects caused a significantly greater fall in outflow facility and rise in outflow resistance than either water drinking alone or homatropine alone ($0{\cdot}02 < P < 0{\cdot}05$ in each case). When applanation tension was considered, water drinking combined with gutt. homatropine again gave the greatest rise; this was again significantly greater than the rise in applanation tension after either water alone or gutt. homatropine alone ($P < 0{\cdot}01$ in each case). This less marked inter-test difference in change in outflow (*i.e.* $0{\cdot}02 < P < 0{\cdot}05$) compared with change in applanation tension (*i.e.* $P < 0{\cdot}01$) is likely to have been due to a wider scatter of tonographic than of tonometric readings. The difference between mean rise in applanation tension and mean rise in outflow resistance cannot unfortunately be compared statistically because they are expressed in different units.

Objectives of present study

I. As a preliminary, the timing of the peak applanation tension after water drinking and gutt. homatropine 2 per cent. was carried out in twenty subjects.

II. In order to assess the relative merits of a tonometry (applanation) test and an outflow (tonography) test, another twenty subjects each had a water-drinking homatropine applanation test and a water-drinking homatropine tonography test in randomized order.

III. The effect of some ocular dimensions on the results of the tests was studied.

Methods

I. Timing of peak applanation tension after water drinking and gutt. homatropine in twenty subjects

(1) SUBJECTS

(*a*) Ten open-angle glaucoma suspects. These had "raised" ocular tension and/or discs considered to be symptomatic of glaucoma.

(*b*) Two cases of open-angle glaucoma.

(*c*) Eight first-degree relatives of patients with open-angle glaucoma.

All had open angles which were judged not to be liable to closure by mydriasis. There were ten males and ten females, and their average age was 50·6 yrs (range 20 to 83).

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(2) PROCEDURE Only one eye chosen at random was used.
Each subject was tested as follows in the course of a morning, having been instructed to have nothing by mouth from midnight on the previous day:

(*a*) Applanation tension.
(*b*) Water by mouth (20 ml./kg. body weight within 5 min.) and gutt. homatropine 2 per cent. to the test eye.
(*c*) Repeat applanation tensions 15, 30, 45, and 60 min. after the end of (*b*).

II. Water-drinking combined with gutt. homatropine. Applanation test compared with tonography test in twenty subjects

(1) SUBJECTS

(*a*) Fourteen open-angle glaucoma suspects who had "raised" ocular tensions and/or optic discs considered symptomatic of glaucoma.
(*b*) Five first-degree relatives of patients with open-angle glaucoma.
(*c*) One patient with unilateral open-angle glaucoma; the apparently normal eye was selected for investigation.

All had open angles which were judged not to be liable to closure by mydriasis. There were thirteen males and seven females and their average age was 57·4 yrs (range 35 to 79).

(2) PROCEDURES

(*a*) *Water-drinking homatropine applanation test*

(*i*) Applanation tension
(*ii*) Water (20 ml./kg. body weight) by mouth within 5 min. and gutt. homatropine 2 per cent. to the test eye
(*iii*) Applanation tension 45 min. after the end of (*ii*)

(*b*) *Water-drinking homatropine tonography test*

(*i*) Applanation tension
(*ii*) Schiotz tonometry
(*iii*) 4-min. tonography
(*iv*) Water (20 ml./kg. body weight) by mouth within 5 min. and gutt. homatropine 2 per cent. to the test eye
(*v*) Applanation tension 45 min. after the end of (*iv*)
(*vi*) Schiötz tonometry
(*vii*) 4-min. tonography

Only one (the same) eye was investigated on each occasion. Each test was done in the course of one morning by a technician who used the Goldmann applanation tonometer and Schwarzer electrotonometer, the 5·5 g. weight being used throughout. The order in which the tests were done was randomized so that, of the twenty patients investigated, ten had the applanation test first and ten the tonography test first. In these two groups of ten patients, five had the right eye tested and five the left. Patients were instructed to have nothing by mouth from midnight on the previous day.

(3) OCULAR DIMENSIONS

In eighteen of the twenty subjects mentioned in *II* (1) above, various ocular dimensions were taken from the eye which received provocation, *viz*:

(*i*) Corneal diameter (from a colour photograph)
(*ii*) Anterior chamber depth (by the No. II Haag-Streit depth-measuring attachment)
(*iii*) Keratometry (Zeiss apparatus)
(*iv*) Lens thickness and vitreous length by A-scan ultrasonography
(*v*) Axial length (=anterior chamber depth + lens thickness + vitreous length)

No patient had received eye drops (*e.g.* gutt. pilocarpine) before the above dimensions were measured.

Results and discussion

I. Timing of peak applanation tension after water drinking and gutt. homatropine in twenty subjects

Fig. 1 shows the mean applanation tension in twenty subjects immediately before, and 15, 30, 45, and 60 min. after water drinking and gutt. homatropine. The mean applanation tension at 30 and 45 min. was the same, so the peak probably occurred at one of these times or between the two. The rise in applanation tension after 45 min. was significantly greater than that after 15 min. ($0{\cdot}01 < P < 0{\cdot}02$: Wilcoxon test). Drance (1963), however, found in a water-drinking applanation test that the maximum rise in applanation tension occurred most frequently 10 min. after the water; he used water only, while our test adds gutt. homatropine. Armaly (1970) found a peak applanation tension 30 min. after water in normal subjects.

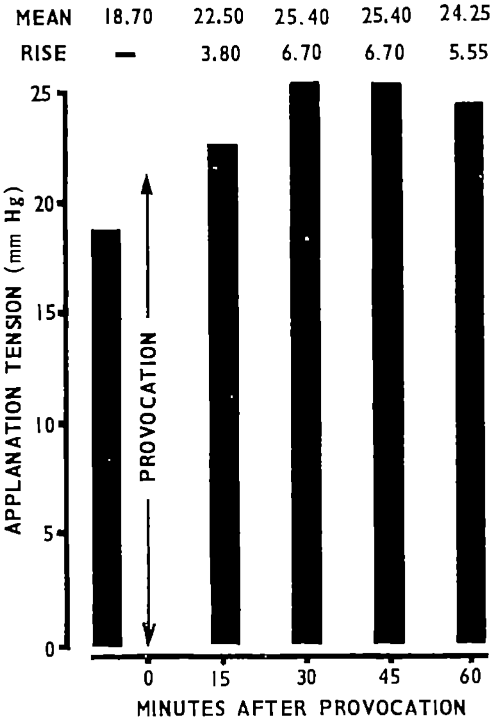

FIG. 1 *Twenty subjects. Water-drinking homatropine applanation test. Mean applanation tensions immediately before, and* 15, 30, 45, *and* 60 *min. after provocation. The peak applanation tension occurred at or between* 30 *and* 45 *min. The rise in applanation tension was significantly greater after* 45 *than after* 15 *min.* ($0{\cdot}01 < P < 0{\cdot}02$)

A higher maximum applanation tension was reached significantly later than a lower maximum applanation tension; $r_s + +0{\cdot}455$, $0{\cdot}01 < P < 0{\cdot}05$ (Fig. 2, overleaf). Inspection of the Tables given by Drance (1963) suggested a similar finding.

The amount of the rise in applanation tension found after 45 min. correlated significantly with age ($r_s = +0{\cdot}526$; $0{\cdot}01 < P < 0{\cdot}05$), *i.e.* the higher rise occurred in older people, as Armaly (1970) also found. No significant correlation was found between the timing of the PEAK applanation tension and age ($r_s = -0{\cdot}059$; $P > 0{\cdot}05$).

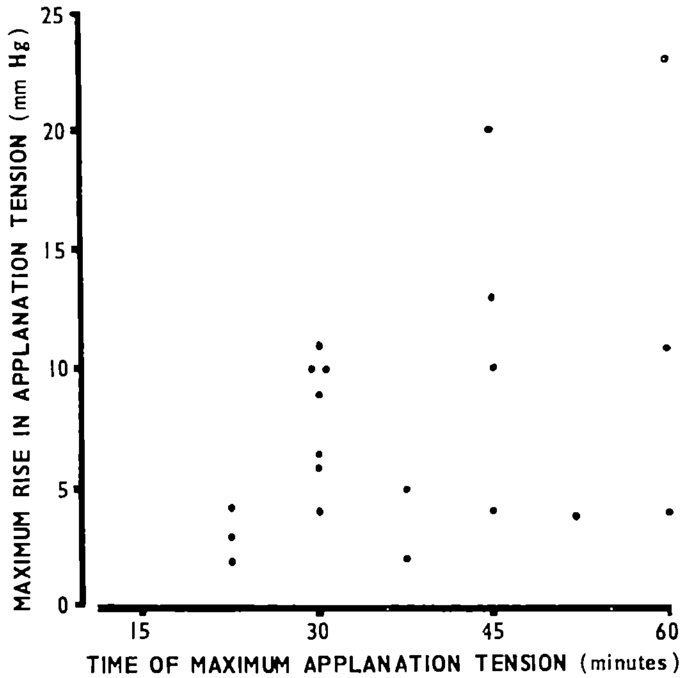

FIG. 2 *Twenty subjects. Scattergram of maximum rise in applanation tension and its timing in a water-drinking homatropine applanation test. A significant correlation was present,* i.e. *the higher the rise, the later it occurred* (r_s = +0·455; 0·01 < P < 0·05)

II. Provocation using water drinking combined with gutt. homatropine: comparison of an applanation test and a tonography test in twenty subjects

(a) RISE IN APPLANATION TENSION AND RISE IN OUTFLOW RESISTANCE DUE TO WATER DRINKING AND HOMATROPINE

Table I shows that the rise in applanation tension in the applanation test and rise in outflow resistance in the tonography test (N.B. at different visits) had both been significant (Student's 't' = 7·47 and 3·98 respectively; P < 0·001 for each). The Wilcoxon test also showed that the rise in applanation tension and rise in outflow resistance had been significant (T = 0 and 12 respectively; P < 0·01 for each). Unfortunately, no statistical test is available to determine which is the more significant rise, or even which is the more significant proportionate rise, although t in the Student's 't' test and T in the Wilcoxon test both suggested that the rise in applanation tension had been slightly more significant

Table I 20 *subjects. Comparison of rise in applanation tension and rise in outflow resistance*

Provocative test	*Water-drinking homatropine test*							
	Applanation				*Tonography*			
Statistical test	*Wilcoxon*		*Student's t*		*Wilcoxon*		*Student's t*	
	T	*P*	*t*	*P*	*T*	*P*	*t*	*P*
Rise in applanation tension	0	<0·01	7·47	<0·001	0	<0·01	6·53	<0·001
Rise in outflow resistance					12	<0·01	3·98	<0·001

T represents the Wilcoxon score for each
t indicates that a Student's 't' test was used

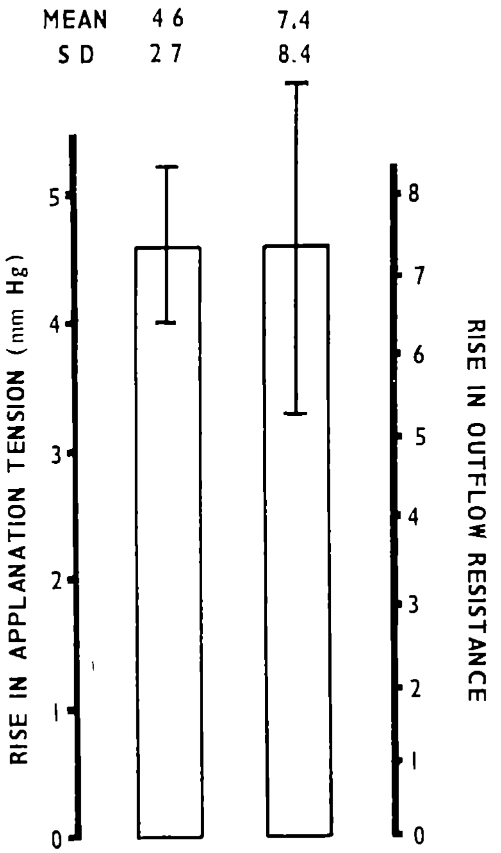

FIG. 3 FIRST COLUMN. *Rise in applanation tension and standard error* I *in water-drinking homatropine applanation test*

SECOND COLUMN. *Rise in outflow resistance and standard error* I *in water-drinking homatropine tonography test*

Note the greater scatter in the second test

than the rise in outflow resistance. In Fig. 3 the rise in applanation tension and rise in outflow resistance are represented in bar charts with the standard error of the mean included for each. Scatter in the rise in outflow resistance is noticeably greater than it is for rise in applanation tension, but again no statistical test is available to compare these measurements.

The rise in applanation tension in the applanation test did not correlate with age ($r_s = -0{\cdot}130$; $P > 0{\cdot}05$), but the rise in outflow resistance in the tonography test ($r_s = +0{\cdot}402$; $0{\cdot}01 < P < 0{\cdot}05$) was age-dependent.

(b) RISE IN APPLANATION TENSION DURING (I) THE APPLANATION TEST, AND (II) THE TONOGRAPHY TEST

In the applanation test itself the mean applanation tension at the end of 45 min. had risen by 4·5 mm. from its initial level of 18·5 mm. The mean applanation tension during the tonography test at the end of 45 min. had risen by 3·9 mm. from an initial 19·2 mm. ($t = 7{\cdot}47$ and 6·53 respectively; $P < 0{\cdot}001$ for each). Surprisingly, the applanation tension 45 min. after provocation seems to have been little influenced by the fall in ocular tension due to the initial tonography.

The rise in applanation tension during the tonography test correlated significantly with that in the applanation test itself at different visits ($r_s = +0{\cdot}498$; $0{\cdot}01 < P < 0{\cdot}05$) and also with the rise in outflow resistance at the same visit $r_s = +0{\cdot}464$; $0{\cdot}01 < P < 0{\cdot}05$).

However, it is an odd finding that the rise in applanation tension in the applanation test and rise in outflow resistance in the tonography test I.E AT DIFFERENT VISITS, did not correlate significantly ($r_s = +0{\cdot}248$; $0{\cdot}2 < P < 0{\cdot}3$).

Two factors may account for this:

(*a*) The tonography test measures a different characteristic from the applanation test (but at the SAME visit the tonometry and tonography results correlated!)

(*b*) A test result depends to some extent on the patient's general state of hydration, etc., at the time of the test (but the applanation results at DIFFERENT times correlated!)

III. *Ocular dimensions and effects of tests*

Table II (opposite) shows correlations between ocular dimensions and rise in applanation tension in both the applanation and tonography tests, and rise in outflow resistance in the tonography test (for further details, see Leighton and Tomlinson, 1971). However, relevant to a comparison between an applanation test and a tonography test are:

(A) WATER-DRINKING HOMATROPINE APPLANATION TEST

A significant correlation between corneal astigmatism and rise in applanation tension was found in that "with-the-rule" astigmatism, *i.e.* smaller vertical than horizontal corneal radius, was associated with a high rise in applanation tension. The direction of the trend is opposite to that between corneal astigmatism and age (Marin-Amat, 1956) and may indicate an unreliable feature of the test because "with-the-rule" corneal astigmatism is unlikely to be a special characteristic of the eye in open-angle glaucoma. An inverse correlation between axial length and rise in applanation tension did not quite reach significance.

(B) WATER-DRINKING HOMATROPINE TONOGRAPHY TEST

(*i*) *Rise in applanation tension*

The correlation with corneal astigmatism was significant ($r_s = -0{\cdot}490$; $0{\cdot}01 < P < 0{\cdot}05$) as it had been in (A), the water-drinking homatropine applanation test.

The following correlations were also significant ($r_s = -0{\cdot}632$; $-0{\cdot}604$ respectively; $P < 0{\cdot}01$ each):

(α) between shallow anterior chamber and a high rise in applanation tension

(β) between great axial length and a small rise in applanation tension.

These last two correlations were not significant in the water-drinking homatropine applanation test (although the same trends were present), probably because the 4-min. tonography expresses fluid and this magnifies the effect on the rise in applanation tension of the surface area of the corneo-scleral envelope.

As an association between shallow anterior chamber and short axial length nearly reached significance ($r_s = +0{\cdot}375$; $P > 0{\cdot}05$; r_s for $P = 0{\cdot}05$ is $0{\cdot}399$), it may well be that shallow anterior chamber was less important than short axial length (Leighton and Tomlinson, 1971) or, more directly, surface area of the corneo-scleral envelope (see Phillips and Shaw, 1970) in determining the effect of the provocation. A greater rise in applanation tension tended to be found in eyes with a small corneal diameter but this trend did not approach significance ($r_s = -0{\cdot}111$; $P > 0{\cdot}05$). However, as shallow anterior chamber was associated with small corneal diameter ($r_s = +0{\cdot}519$; $0{\cdot}01 < P <$

Table II 18 *Subjects. Correlations between* (1) *Ocular dimensions and age and* (2) *effects of water drinking and gutt. homatropine on applanation tension and outflow resistance*

Test	*Rise in*	*Correlation coefficients between rise in applanation tension or outflow resistance and:* *Corneal diameter*	*Horizontal corneal radius*	*Astigmatism (corneal radii: horizontal minus vertical)*	*Anterior chamber depth*	*Lens thickness*	*Vitreous length*	*Axial length*	*Age*
Water-drinking	Applanation	−0·369	+0·150	−0·482	−0·150	−0·232	−0·031	−0·232	−0·276
(*a*) Homatropine applanation	tension	NS	NS	S*	NS	NS	NS	NS	NS
Water-drinking	Applanation	−0·111	+0·273	−0·490	+0·632	−0·278	−0·354	−0·604	+0·040
(*b*) (*i*) Homatropine tonography	tension	NS	NS	S*	*S*	NS	NS	*S*	NS
Water-drinking	Outflow	−0·088	−0·190	−0·084	−0·112	+0·503	−0·296	−0·250	+0·309
(*b*) (*ii*) Homatropine tonography	resistance	NS	NS	NS	NS	S*	NS	NS	NS

S = Significant at $P < 0·01$
S* = Significant at $0·01 < P < 0·05$
NS = Not significant $P > 0·05$

Correlation coefficient for P = 0·05 is 0·399
and for P = 0·01 is 0·564

The rise in applanation tension in (*a*) is the difference between applanation tensions taken immediately before and 45 min. after provocation.

The rise in applanation tension in (*b*)(*i*) and rise in outflow resistance in (*b*)(*ii*) are the differences between tonometric and tonographic readings taken immediately before and 45 min. after provocation. (*b*)(*i*) and (*b*)(*ii*) relate to the same visit.

0·05), the latter could also have contributed to the correlation found between shallow anterior chamber and a high rise in applanation tension after the provocation. Presumably the high rise in applanation tension after provocation in an eye with a small corneal diameter *and circumference* is due to the relatively small cross-sectional area of outflow channels available for escape of aqueous in such eyes.

Correlation between a small rise in applanation tension and high axial length seems an unfortunate trend in a test to diagnose glaucoma, because large eyeballs have significantly greater applanation tensions than small eyeballs (Tomlinson and Phillips, 1970), which is consistent with the observations that myopic eyes are probably unduly prone to open-angle glaucoma (Weekers, Lavergne, and Prigot, 1958; Perkins and Jay, 1960). Probably the small surface area of corneo-scleral envelope in an eye with a short axial length is less able to accommodate the increased volume of aqueous humour formed after water drinking.

(*ii*) *Rise in outflow resistance*

The only significant correlation was with lens thickness, the explanation for which (Leighton and Tomlinson, 1971) is presumably an indirect one, *e.g.* correlation of both rise in outflow resistance and lens thickness with age, although it may be due to the association of a thick lens and a shallow anterior chamber and hence a narrow angle, which may be correlated with high outflow resistance (François, Rabaey, Neetens, and Evens, 1958).

Further discussion and conclusions

The noticeably greater variance of the rise in outflow resistance compared with the rise in applanation tension (Fig. 3) is likely to be a disadvantageous feature of a water-drinking homatropine *tonography* test if used in the diagnosis of open-angle glaucoma. On the other hand, the high variance of the rise in outflow resistance may merely have revealed more effectively the heterogeneity of the sample, some of which may be due to attributes of the eye in open-angle glaucoma, although all the test subjects lacked pathological cupping of the optic discs and field defects typical of glaucoma.

The correlations between rise in applanation tension and rise in outflow resistance and (α) shallowness of the anterior chamber (probably due to) (β) small axial length (an unreliable trend?) were not noticeably different: see Table II. (None was significant.)

A significant correlation was found between (*i*) a high rise in applanation tension in the water-drinking homatropine *tonography* test and (*ii*) short axial length. This trend was not significant in the water-drinking homatropine applanation test. This discrepancy probably indicated that the squeezing-out effect of the initial tonography had magnified a tendency for the effect of the provocation to be dependent on surface area of corneo-scleral envelope (Phillips and Shaw, 1970).

Mainly because of the greater scatter of the tonography readings, it seems reasonable to conclude that *a water-drinking homatropine applanation test is marginally better than a water-drinking homatropine tonography test.* An applanation test is easier to perform. However, in the final analysis, the relative ability of these two tests to discriminate between normal subjects and patients predisposed to open-angle glaucoma would have to be assessed by a protracted long-term study of cohorts. Nevertheless it seems practical to avoid provocative tests involving tonography, which is an inconsistent test even in the same individual (Gloster, 1966), in open-angle glaucoma and to proceed in a future study to compare the normal and glaucomatous response to the water-drinking homatropine applanation test.

Summary

In twenty subjects (ten open-angle glaucoma suspects, two cases of open-angle glaucoma, and eight first-degree relatives of patients with open-angle glaucoma), the rise in applanation tension after water drinking (20 ml./kg. body-weight) combined with gutt. homatropine 2 per cent. was significantly greater after 45 than after 15 min. ($0{\cdot}01 < P < 0{\cdot}02$). The maximum rise occurred at or between 30 and 45 min. after the provocation. A high maximum applanation reading tended to occur significantly later than a low maximum ($0{\cdot}01 < P < 0{\cdot}05$).

Another twenty subjects (fourteen open-angle glaucoma suspects, five first-degree relatives of patients with open-angle glaucoma, and one patient with "unilateral" open-angle glaucoma) each had a water-drinking homatropine applanation test and a water-drinking homatropine tonography test in random order on one eye. The effects of the provocation were measured by a second applanation or tonography reading 45 min. after the provocation. *The applanation test was considered marginally better than the tonography test* because the *rise* in applanation tension in the former was slightly more significant than the *rise* in outflow resistance, and the scatter of the rise in applanation tension was noticeably smaller than the scatter of the rise in outflow resistance. It is therefore planned to compare the effects of a water-drinking homatropine applanation test on normal subjects and patients with open-angle glaucoma.

The older the patient the higher the rise in applanation tension in response to water drinking plus homatropine (significant at $0{\cdot}01 < P < 0{\cdot}05$).

The rise in *applanation tension* in the water-drinking homatropine *tonography* test, *i.e.* when a 4-min. tonography had been done after the initial applanation tension (before provocation), tended to be higher if the axial length was short (significant correlation $P < 0{\cdot}01$), probably because the squeezing-out effect of the initial tonography magnified a tendency for the effect of provocation to be dependent on the surface area of the corneo-scleral envelope.

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Intermittent exophthalmos

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The syndrome of intermittent exophthalmos classically consists of enophthalmos with the head in the upright position, and exophthalmos which develops rapidly in one eye (usually the left) when venous stasis is induced by bending or lowering the head, turning the head forcibly, hyperextension of the neck, coughing, forced expiration with or without compression of the nostrils, or pressure on the jugular veins. The condition is often referred to as orbital varix, varicocele, venous aneurysms, or arterio-venous aneurysm (Walsh and Dandy, 1944; Brauston and Norton, 1963).

Cases of intermittent exophthalmos have been reported by Birch-Hirschfeld (1930), Wissmann and Schulz (1922), Rumjanzewa (1930), Bartók (1931), de Petri (1935), Marchesini (1935), Hippert (1936), Muirhead (1936), Kraupa and Mendl (1936), Lipowitsch (1936), Petrov (1939), Spektor (1939), Giquéaux (1942), Poole (1942), Dunphy (1942), Rones (1942), and Walsh and Dandy (1944).

Orbital varices constitute about 90 per cent. of cases of intermittent proptosis (Duke-Elder, 1952). Recurrent orbital haemorrhages may also cause intermittent proptosis (Meyer, 1898; Teillais, 1898; Gayet, 1899), and highly vascular orbital neoplasms, such as angioma (von Graefe, 1866; Hegner, 1915; Augstein, 1917; von Hippel, 1918), lymphangioma (Wintersteiner, 1898; Franklin and Cordes, 1924; Wolff, 1932), lymphosarcoma (Perzewa, 1922), and retrobulbar venous cavernous haemangioma (Zeidler and Zetterström, 1959) are other lesions which may give rise to this condition.

Intermittent proptosis accompanied by chemosis may be caused by venous congestion; this is sometimes seen during menstruation (Krauss, 1910; Morelli, 1922; Kragh and Holm, 1923), during the strain of childbirth (Rumjanzewa, 1930), or during a paroxysm of crying in infants which leads to spasm of the orbicularis, and may even result in dislocation of the globe (Duke-Elder, 1952). The condition may also occur if thrombosis of the cavernous sinus reduces the efficiency of the venous return from the orbit.

Other rare causes of intermittent proptosis are periodic orbital oedema (particularly of the angioneurotic type), recurrent emphysema (Duke-Elder, 1952), intermittent ethmoiditis (Selkin, 1925; Benoit, 1926; Juler, 1932), and intermittent otitis (Eagleton, 1935).

Case report

A young woman aged 21 years came to the Out-patients Clinic of the Ophthalmic Hospital at Tanta, complaining of protrusion of the left eye on bending the head downwards or stooping, accompanied by pain in the eye and headaches. The condition had started gradually 2 years before, with protrusion of the left eye whenever the patient lowered her head, but recovery immediately the head was raised. Pain and headaches had begun to appear only 6 months previously and occurred whenever the eye protruded.

There was no history of trauma, cough, sinusitis, or fever, but the condition had first appeared after the patient's second labour.

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Examination

The eyes were myopic, with a temporal myopic crescent in the fundus. The visual acuity was 1/60 in both eyes without glasses, and 6/24 with correction—10 D sph. in the right eye and —9 D sph. in the left.

The left eye showed enophthalmos when the head was upright (Fig. 1). Bending the head slightly forwards caused a moderate protrusion of the left eye (Fig. 2), and lowering the head downwards was immediately followed by a marked protrusion of the left eye (Table), which recovered when the head was raised. Lateral rotation of the head also produced protrusion of the left eye (Fig. 3). The proptosis was non-pulsatile and non-reducible. The movements of the eyeball were normal. Narrowing of the palpebral fissure was noticed during the episodes of protrusion (Fig. 4). There was no change in the fundus appearance during the protrusion. No dilated veins were evident on the lids or face.

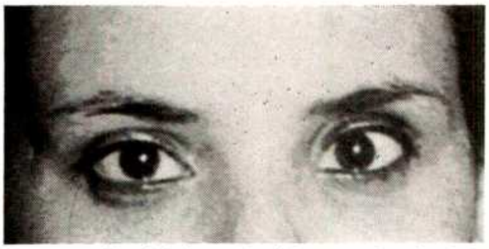

FIG. 1 *Enophthalmos in left eye when head is upright*

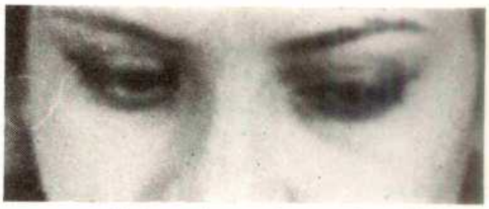

FIG. 2 *Moderate degree of protrusion of left eye, when head is bent slightly forwards*

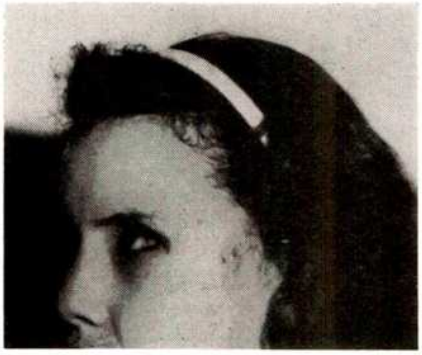

FIG. 3 *Protrusion of left eye with lateral rotation of head*

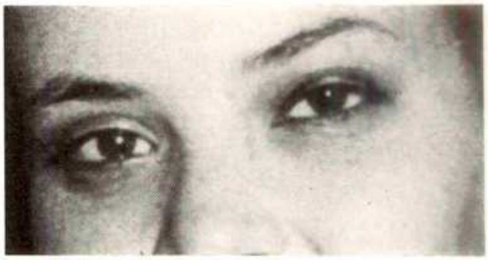

FIG. 4 *Narrowing of left palpebral fissure during protrusion of left eye*

Table *Exophthalmometric measurements with the head in different positions*

Position of head	*Exophthalmometric measurement (mm. Hertel)*	
	Right eye	*Left eye*
Upright	17	15
Bending slightly forwards	17	21
Lowering head downwards	18	25
Turning laterally	17	22

Investigations

Systemic and ear, nose and throat examinations revealed no abnormality. There was no evidence of any endocrine disturbance.

X rays of the skull, orbits, and paranasal sinuses appeared normal. The basal metabolic rate and blood picture were also normal. Arteriography and phlebograms of the orbital veins were not performed as facilities were not available.

Discussion

Krauss (1910) assumed that the presence of large congenital orbital varicosities and any obstruction to the drainage of orbital blood, either anteriorly or posteriorly, could produce intermittent exophthalmos.

Brauston and Norton (1963) stated that the exophthalmos was due to a "vascular lake" behind the globe, probably congenital or developmental in origin. This could lie entirely within the orbit, or be connected with the cranial cavity; it emptied in the upright position and filled with any obstruction in the venous drainage.

The condition is usually progressive, and the most frequent complaint, which is common in the second or third decade, is fullness, bulging, and pain in the involved eye together with dizziness and vertigo when the patient bends forwards, or when there is impairment of the venous return from the head (Walsh and Dandy, 1944; Brauston and Norton, 1963). Birch-Hirschfeld (1930) suggested that the presence of intracranial varices might account for these symptoms.

All the reported cases have been unilateral. Poole (1942) remarked that the left eye was involved ten times more than the right, and Reese (1935) pointed out that the left jugular foramen is frequently smaller than the right.

Birch-Hirschfeld (1930) observed the occurrence of intermittent exophthalmos in relation to the various positions of the head. A latent period of 5 seconds was followed by a protrusion of the eye when the head was bent forwards, which reached its maximum in 30 seconds. Lateral rotation of the head was also found to influence the position of the eye, owing to a degree of jugular constriction. Proptosis can also be produced by pressure over the jugular vein on the affected side (Walsh and Dandy, 1944). Mulder (1900) reported a case which was evident only when the patient wore a tight collar.

Enophthalmos is usually apparent only when the head is in the erect position, and is due to the absorption of the orbital fat from long-standing pressure of the vascular bed in the orbit (Walsh and Dandy, 1944).

Narrowing of the palpebral fissure during the episodes of exophthalmos was observed by Poole (1942), Rumjanzewa (1930), and Walsh and Dandy (1944). Pupillary dilatation has also been described by several observers, although Rumjanzewa (1930) observed narrowing of the pupil in her case.

Walsh and Dandy (1944) noticed overfilling of the retinal veins, which pulsated during the protrusion; but otherwise the fundus was usually normal. In no instance have there been dilated veins over the lids, face, and scalp, such as are commonly observed in cases of carotid-cavernous fistula and cirsoid aneurysm. Pulsations of the eyeball are rare.

The involved eye in most cases remains normal, although optic atrophy was noticed by Birch-Hirschfeld (1930) in 14 per cent. of cases; this he claimed to be due to retrobulbar haemorrhage which was an occasional complication. Walsh and Dandy (1944) suggested that the optic atrophy could be due to long sustained-direct pressure of the vascular mass on the optic nerve.

X rays have usually been reported as negative. An enlarged superior orbital fissure was noted by Walsh and Dandy (1944), and an enlarged orbit by Jones (1961). The presence of phleboliths was reported by Kraupa and Mendl (1936), Teitgen and Benedict (1951), Hu Yung-Lin and Shih Chen-Jung (1954), and Hager (1958).

Arteriography, which has rarely been performed proved negative on two occasions (Uberall, Schweitzer, and Gonzalez, 1955; Zeidler and Zetterström, 1959). One case revealed an intraorbital arteriovenous aneurysm without intracranial extension (Jacas, Ley, and Campillo, 1959).

Phlebograms of the intraorbital veins have recently been carried out *via* the angular vein in a case of intermittent exophthalmos by Krayenbühl (1962), who noticed a "cherry-like enlargement of the superior ophthalmic vein".

The first surgical procedure was performed by Schimanowsky (1907), who clamped the superior ophthalmic vein in the back of the orbit, through an incision beneath the eyebrow. Other attempts to ligate the dilated veins in the orbit were performed by Löwenstein (1911), Germain and Weill (1927), Rumjanzewa (1930), and Brauston and Norton (1963). Serious complications were encountered in some cases, such as spontaneous severe haemorrhage (Löwenstein, 1911) and post-operative external ophthalmoplegia with enophthalmos (Germain and Weill, 1927).

Brauston and Norton (1963) advised that, if the orbital fissure was normal and arteriography and phlebography did not demonstrate any intracranial extension, the varix might be isolated and excised by an orbital approach, but if the sphenoidal fissure was enlarged or there was arteriographic evidence of intracranial extension, the transcranial approach of Walsh and Dandy (1944) should be preferred. They observed, however, that "it may be impossible to remove such a vascular anomaly without causing irreparable damage to the function of the globe".

The injection of sclerosing solutions into the orbital veins has been advocated by several authors (Raverdino, 1925; Hippert, 1936; Tanzi, 1948; Sená, 1955), but there is always the risk of serious sequelae if intracranial extensions exist (Brauston and Norton, 1963).

Summary

A case is reported of intermittent exophthalmos due to an orbital varicocele, which developed after labour.

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Diagnosis of ocular myopathy

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Hutchinson (1897) described a disorder in which ptosis was associated with paralysis of the other extraocular muscles to which he gave the name "external ophthalmoplegia". Fuchs (1890) reported five patients with ptosis, in two of whom the disorder was familial, and Dutil (1892) and Delord (1903) published two other cases of an unusual familial form of dysphagia associated with ptosis. The prevailing opinion at the time was that external ophthalmoplegia was due to a degeneration of cranial nerve nuclei. The idea that ptosis was but a fragment of a progressive dystrophy of all striated ocular muscles was put forward by Treacher Collins (1922) and by Sandifer (1946). This opinion has gained acceptance only since the critical study of Kilch and Nevin (1951), in which five patients with progressive muscular dystrophy with early and predominant affection of the external ocular muscles were described; they suggested that the term "ocular myopathy" be applied to these cases.

Lees and Liversedge (1962) described three examples of the descending form of this disease. In their cases the ptosis and ophthalmoplegia preceded by many years the involvement of the face, pharynx, larynx, neck, shoulder, and pelvic girdles, and the course of the illness was slow and relatively benign. Victor, Hayes, and Adams (1962) called attention to a form of restricted myopathy of cranial muscles characterized by dysphagia and ptosis which they called oculopharyngeal myopathy; both familial and sporadic cases were described and firm evidence was presented that the disorder was myopathic. Roberts and Bamforth (1968) analysed 26 further patients diagnosed as cases of ocular myopathy; six of their patients had dysphagia with motility and radiographic changes suggesting that the dystrophic process also involved the smooth muscle of the oesophagus.

Because of the apparent rarity and lack of general recognition of ocular myopathy, we thought it of interest to describe four cases seen over the course of one year.

Case reports

Case 1, a 22-year-old single woman, developed drooping of the eyelids at the age of 11 years. She had two operations to correct this at the ages of 11 and 15 years. Her relatives noticed that her eye movements were limited but she had not complained of double vision. She stated that if she talked or read aloud for some length of time her voice became weak. There was no family history of myopathy.

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Examination

There was severe bilateral ptosis, all eye movements were markedly restricted, those of the left eye being less affected; there was 10° of side-to-side movement, no movement above the horizontal, and only 5° downward movement. The pupils were equal and the reactions were normal. This patient also had bilateral weakness of the orbicularis oculi and of the lower facial muscles leading to a mournful expression. There was considerable wasting of the muscles of the neck and she was unable to lift her head up from the pillow. Her tongue was small but there was no myotonia; her voice was weak. Palatal movements appeared to be normal. There was considerable wasting of the muscles of the forearms on both sides. The upper limbs showed asymmetrical weakness, more marked on the right side and affecting especially the trapezii and triceps. There was also weakness of the trunk muscles and of hip flexors. All the tendon reflexes were absent in the upper limbs, but normal in the lower limbs; the plantar responses were flexor.

Investigations

Electromyography of the left lateral rectus was consistent with myopathy, the units on voluntary deviation being of extremely low amplitude (about 20 μV) and rather scanty. Serum creatinine phosphokinase was 116 mU/ml. (normal range for women 5–50 mU/ml.) but the serum aldolase at 0·9 mU/ml. was within the normal range 0–6 mU/ml.

Muscle biopsy of the deltoid (Fig. 1) showed some variation in the size and staining properties of the muscle fibres with minimal degenerative changes affecting single segments rather than the whole fibre. The changes were slight but myopathic in type. It should be noted that the muscle used for biopsy was not clinically affected.

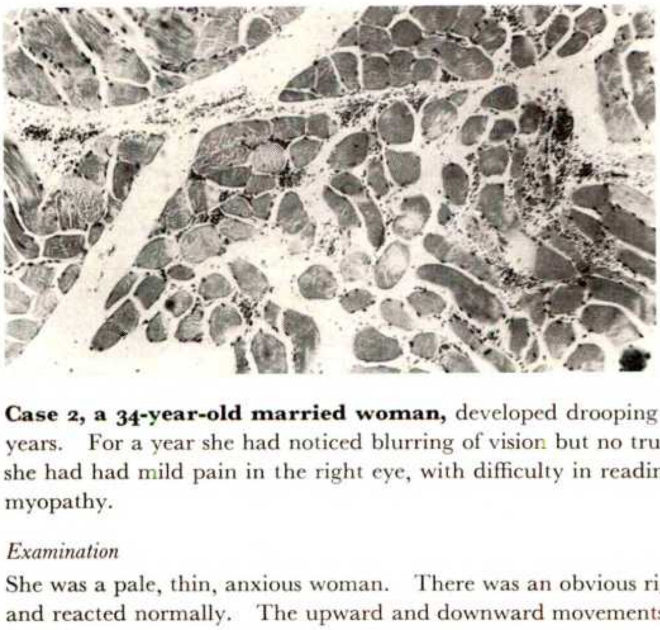

FIG. 1 *Biopsy of deltoid muscle in Case* 1. ×90

Case 2, a 34-year-old married woman, developed drooping of the right eyelid at the age of 25 years. For a year she had noticed blurring of vision but no true diplopia on lifting the eyelid, and she had had mild pain in the right eye, with difficulty in reading. There was no family history of myopathy.

Examination

She was a pale, thin, anxious woman. There was an obvious right ptosis but the pupils were equal and reacted normally. The upward and downward movements of both eyes were full. There was moderate weakness of abduction of the right eye and slight weakness of the left and considerable weakness of adduction of the right eye. There was a little weakness of both orbicularis oculi muscles and definite weakness of the neck muscles and of the right triceps. The tendon reflexes were brisk and equal. Plantar responses were flexor.

Investigations

A tensilon test was negative. Serum creatinine phosphokinase was normal at 39 mU/ml. and the aldolase was within normal limits. The electromyogram was compatible with a mild myopathy.

Muscle biopsy of levator palpebrae (Figs 2 and 3) revealed that the muscles were almost completely destroyed and contained only a few surviving, apparently normal, fibres. The bulk of the specimen consisted of fibres and fatty tissue containing numerous nerve bundles. The good preservation of the latter suggested that the lesion was a myopathy.

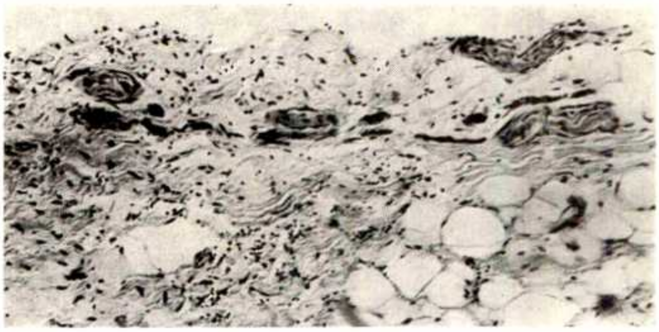

FIG. 2 *Biopsy of levator palpebrae muscle in Case 2.* ×120

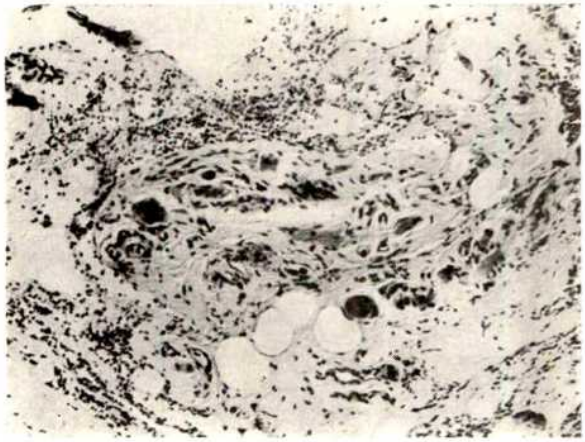

FIG. 3 *Biopsy of levator palpebrae muscle in Case 2.* ×120

Treatment

A surgical repair of the ptosis was made when the muscle biopsy was performed. The patient was satisfied with the result of this operation.

Case 3, a 46-year-old married woman, developed drooping of the right eyelid at the age of 41 years. For the previous 6 months she had complained of aching of the right eye but there was no definite diplopia. There was no family history of myopathy.

Examination

There was moderate right ptosis but the eyelid did not cover the pupil. There was also mild proptosis of the right eye. There was limitation of abduction of both eyes, and of adduction of the right. There was bilateral weakness of the orbicularis oculi and the voice was weak. The neck muscles were also weak and the patient was unable to lift her head from the pillow. The right triceps muscle was slightly weak. The reflexes were brisk and equal; the plantar responses were flexor.

Investigations

A tensilon test was negative. Creatinine phosphokinase was raised 63 mU/ml. Electromyography of the sternomastoid showed only a few short motor units in the right. The motor unit pattern was otherwise normal. Radioactive iodine uptake and serum protein bound iodine were both within normal limits. Muscle biopsy was not done.

Case 4, a 71-year-old man, had developed drooping of the eyelids at 50 years of age. This had been much more marked during the last year, when he had noticed double vision on reading, images being vertically separated. He had also noticed slight weakness of the neck and shoulders. He had been diagnosed as suffering from myxoedema 10 years earlier, and had since taken thyroid tablets (120 mg. a day). There was a family history of ptosis and of haemophilia, as shown in Fig. 4.

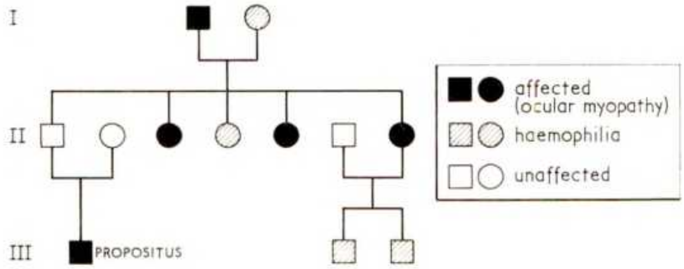

FIG. 4 *Case 4. Family tree*

Examination

He had severe bilateral ptosis (Fig. 5), two-thirds of each pupil being covered by the upper lid. All eye movements were severely restricted; there was less than 5° movement up and down and less than 10° side-to-side. The pupils were equal in size and reacted to light and accommodation. The forehead was constantly wrinkled and the eyebrows were raised above the level of the supraorbital ridges. Both orbicularis oculi muscles were weak and there was slight weakness of the lower face and of both sternomastoids and trapezii. The tendon reflexes were brisk and equal; plantar responses were flexor. Muscle biopsy of the sternomastoid is shown in Fig. 6.

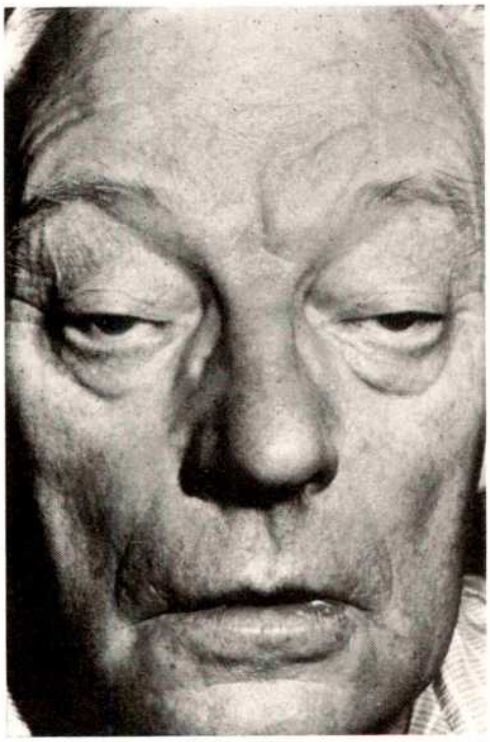

FIG. 5 *Case 4. Bilateral ptosis*

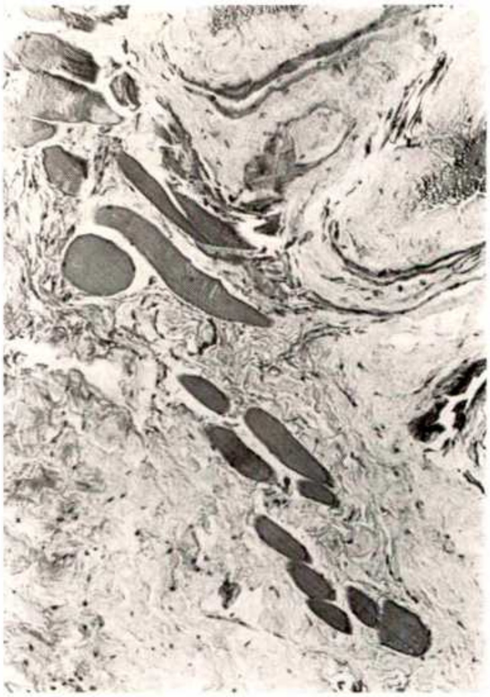

FIG. 6 *Biopsy of sternomastoid muscle in Case 4.* × 100

Investigations

A tensilon test was negative. Electromyogram of the right sternomastoid showed patches of small, short disintegrated myopathic units throughout the muscle. The right deltoid and right quadriceps showed normal activity. Serum creatinine phosphokinase was raised at 82 i.u./litre. Muscle biopsy of the sternomastoid (Fig. 6) showed a considerable increase in the amount of fibrous tissue, which contained a few remaining muscle fibres. Outside the areas of fibrosis the muscles showed no abnormality. These appearances were those of a low grade myopathy.

Treatment

This patient had a bilateral repair of his ptosis and was pleased with the improvement in his ability to see and in his appearance.

Methods of investigation

Investigation of patients with ocular myopathy is reasonably simple and the estimation of serum muscle enzymes is a useful confirmatory test, although these may not always be abnormal if the disease is restricted to a small group of muscles. Muscle biopsy of the external ocular muscles is not easy to perform and not a minor procedure, although it can be combined with correction of the ptosis. It was useful in two of these patients to perform a plastic operation on the eyelid and to take a biopsy of the levator palpebrae simultaneously. Unfortunately the state of this muscle was not entirely satisfactory from the pathological point of view, as the disease process was found to be far advanced by the time of the biopsy. In another patient, in whom a limb girdle muscle was sampled, this showed early changes of muscular dystrophy.

Discussion

Cases 1 to 3 illustrate the descending ocular myopathy of the type described by Lees and Liversedge (1962). As in their cases, there was no family history of any similar condition. In Case 1 the disease was more or less symmetrical but in Cases 2 and 3 it was markedly asymmetrical. Case 2 at first glance resembled a unilateral third nerve palsy and it is of interest that this patient had been investigated as such in a Neuro-surgical Unit by means of carotid arteriograms and air studies. Case 3 had also been misdiagnosed as one of exophthalmic ophthalmoplegia because of slight unilateral proptosis. However, the weakness of the neck and shoulder girdle muscles is out of keeping with this diagnosis unless there is coexistent thyrotoxic myopathy and a definite unilateral ptosis would also be most unusual in this disease. There was no oedema of the eyelids or injection of the conjunctivae and major symptoms of ocular discomfort characteristic of exophthalmic ophthalmoplegia were absent.

Case 4 illustrates a slowly progressive, familial form of this disease. The family tree suggests a dominant mode of inheritance, although the patient's parents were allegedly normal. The disease had progressed slowly over two decades to affect the face, neck, and shoulder muscles as in the other patients.

The most important differential diagnosis in these patients is that of myasthenia gravis. The tensilon test usually distinguishes this condition (edrophonium chloride 10 mg. intravenously). While there may not be much improvement in the power of the external ocular muscles with tensilon, the drooping of the eyelids almost invariably improves with an injection of this substance.

Ophthalmologists should always be on the lookout for this neurological disorder in patients presenting to them with ptosis.

Summary

The literature of ocular myopathy is reviewed. Four cases of this condition are presented and the differential diagnosis discussed.

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Orbital teratoma

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Teratomata are congenital tumours in which representatives of all three germinal layers are found in all degrees of complexity even up to a partially or completely developed foetus (Duke-Elder, 1952). Approximately twenty cases of true teratoma of the orbit have been reported (Burnier and Salles, 1945; Harbert, 1949; Pesme and Maupetit, 1951; Girard, Fountain, Moore, and Thomas, 1958). The following case is reported because of the rarity of this condition.

Case report

A baby girl aged 5 months (Fig. 1) had a left proptosis from birth. Her parents were cousins, and she was their first child. The baby's general condition was good, and there was no other abnormality in her body. The blood Wassermann reaction was negative. A postero-anterior skull *x* ray showed a dilated left orbit but no destruction of the orbital bones.

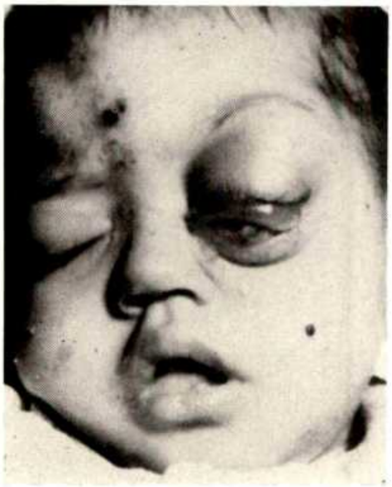

FIG. 1 *Left proptosis due to orbital teratoma, present since birth*

The right eye was normal with a normal fundus. The left eye showed a proptosis of 25 mm. (Hertel) downwards with limitation of upward ocular movements. A soft mass was palpated in the orbit between the eye and the orbital roof. Exploration of the orbit showed a non-encapsulated, soft, pinkish tumour measuring 2 × 2 cm., which was removed.

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Histopathological examination of the tumour showed a teratoma composed of skin with hair follicles and sebaceous glands (Fig. 2), lymphoid tissue (Fig. 3), intestinal mucosa and tubular glands (Fig. 4), and cellular connective tissue with involuntary muscles surrounding the cystic spaces (Fig. 5).

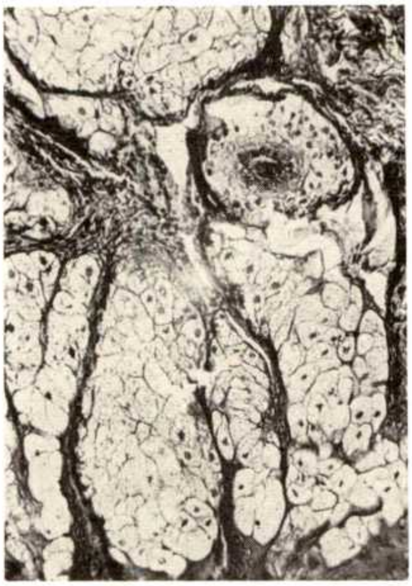


FIG. 2 *Orbital teratoma, showing skin with hair follicles and sebaceous glands.* ×90

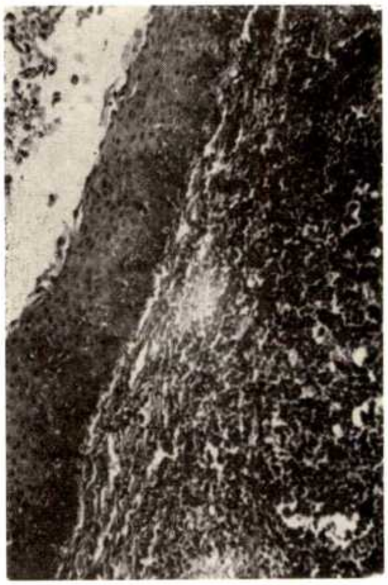


FIG. 3 *Orbital teratoma, showing stratified epithelium and lymphoid tissue.* ×90

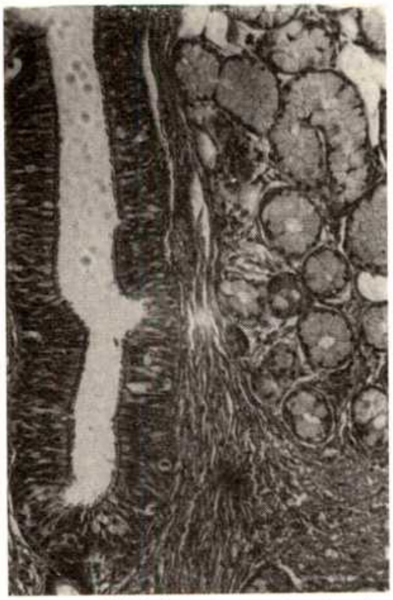


FIG. 4 *Orbital teratoma, showing intestinal mucosa with tubular glands.* ×90

(5)

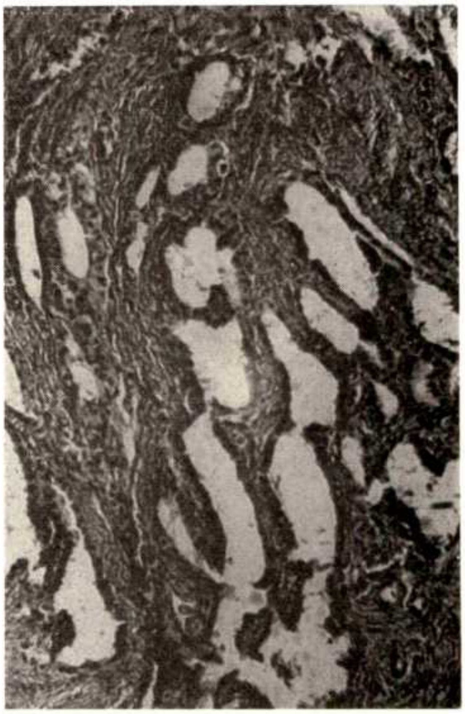
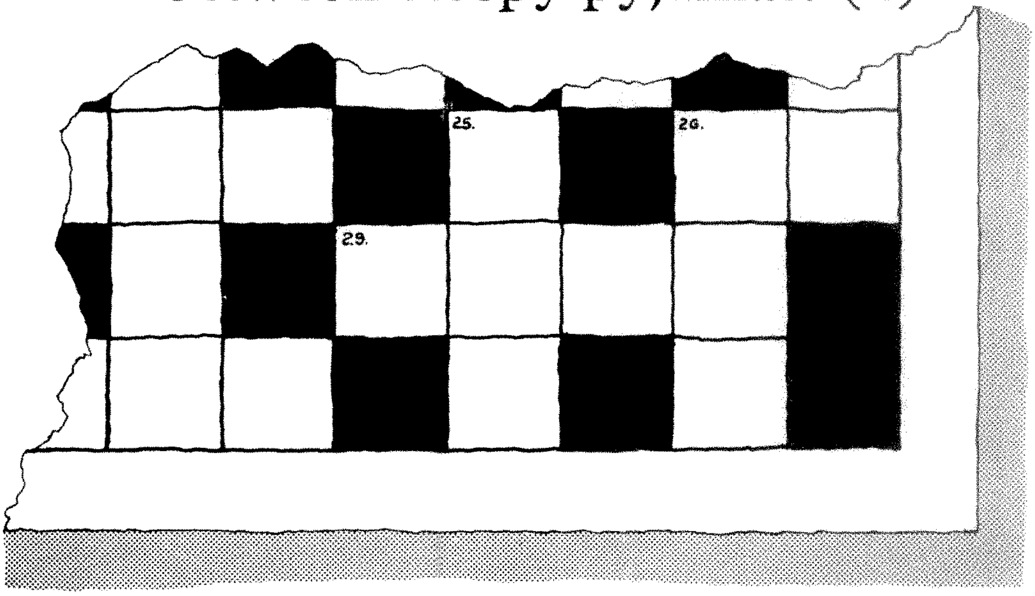


FIG. 5 *Orbital teratoma, showing cellular connective tissue with involuntary muscles surrounding cystic spaces.* ×120

29. **Glaucoma?** Why drop-out between sleepy pyjamas. (4)



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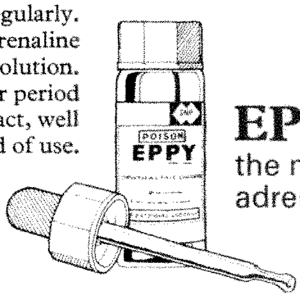

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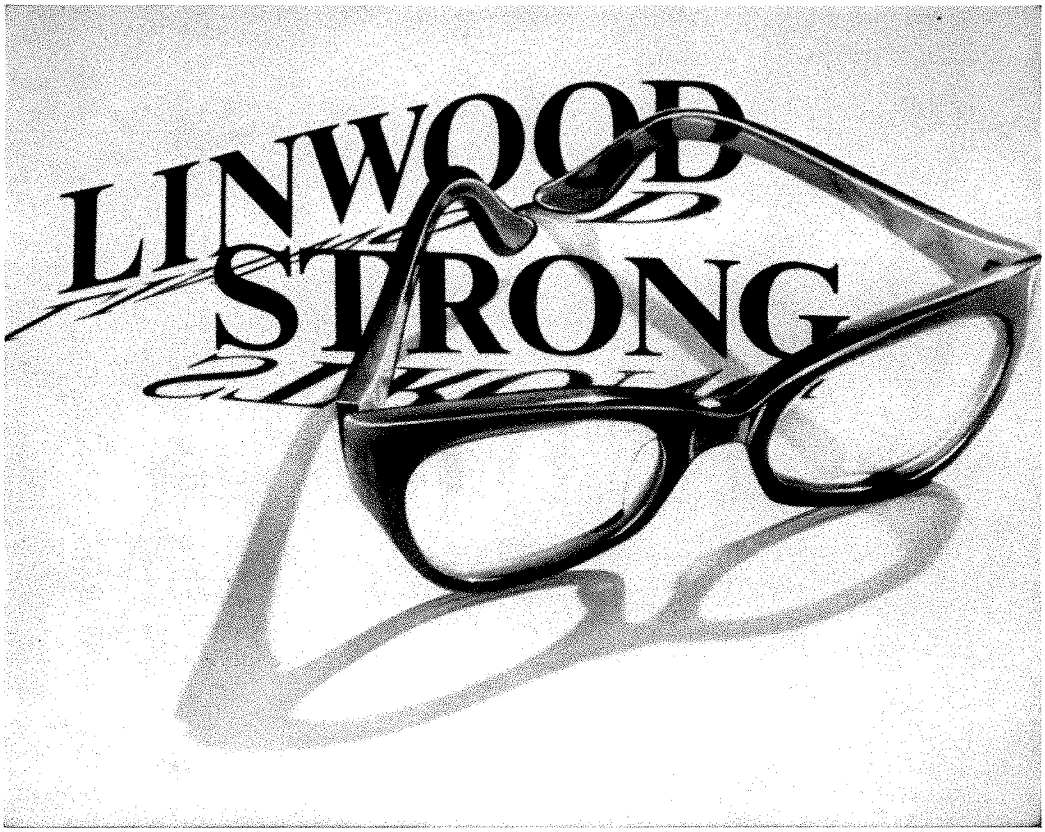

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Summary

(1) In a series of 900 histopathologically proved orbital tumours this is the only teratoma. It was found in the left orbit of a baby girl, whose parents were cousins.

(2) Histopathological examination revealed skin, lymphoid tissue, intestinal mucosa, tubular glands, and involuntary muscles.

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Brit. J. Ophthal. (1971) **55,** 642

Scaphocephaly, bilateral aniridia, and bilateral anterior polar cataract with posterior dislocation of the lens

H. MOHAN, D. K. SEN, AND D. K. GUPTA
Department of Ophthalmology, Irwin Hospital, New Delhi, India

Craniofacial dysostoses are rare conditions in which the growth of the skull is interfered with at right-angles to the obliterated suture and the expanding brain is forced to grow in another direction. These dysostoses have been classified in various ways and the following types have been taken by Duke-Elder (1964) as typical: oxycephaly (tower skull); scaphocephaly (scaphoid head); plagiocephaly (slanting head); trigonocephaly, platycephaly, and hypertelorism. The underlying anomaly seems to be a failure in the development of the primitive mesoderm from which the bones of the skull develop.

The purpose of this paper is to report the occurrence of aniridia with other anomalies in a patient with a craniofacial dysostosis. This association has not previously been reported.

Case report

An 8-month-old baby was brought to the Eye Department of the Irwin Hospital because of an abnormally shaped skull, "shaking" of the eyes, and delayed physical progress. The mother's pregnancy and delivery had been normal and there was no family history of similar defects.

EXAMINATION

The skull was very long in proportion to its width (Figs 1 and 2). There was no frontal bossing and the sagittal suture was prominent to palpation.

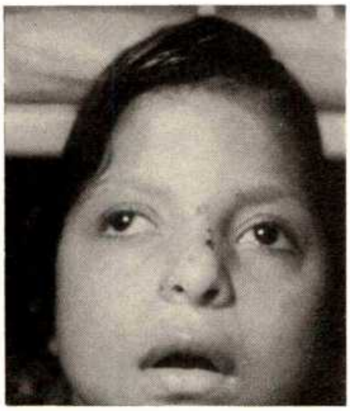

FIG. 1 *Narrow skull and right concomitant divergent squint*

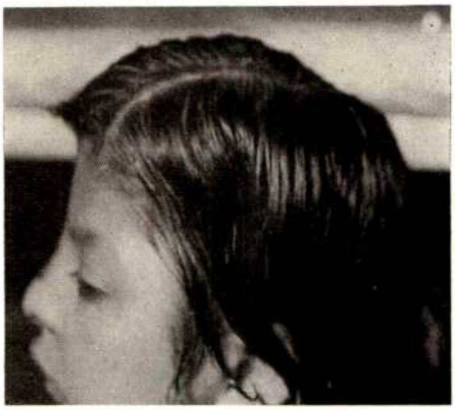

FIG. 2 *Length of skull. Note that there is no frontal bossing*

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Address for reprints: Dr. H. Mohan, 11/B Ganga Ram Hospital Marg, New Delhi 5, India

Both eyes showed a horizontal, pendular, congenital nystagmus, associated with a right concomitant divergent squint of about 20°. The irides were completely absent in both eyes, but gonioscopy revealed a rudimentary iris stump hidden behind the corneo-scleral margin.

A small (diameter 1·5 mm.), flat, circumscribed anterior polar cataract was also present in both eyes. Ophthalmoscopy showed bilateral post-papillar optic atrophy.

Systemic examination revealed no other abnormality, but radiographs showed a typical silver-beaten appearance of the skull with enlargement of the sella and destruction of the posterior clinoid processes. The orbits were shallow.

PROGRESS

The child was brought to us again nearly 2 years later, when the lenses in both eyes were found to be dislocated into the vitreous. There was no history of trauma to account for the dislocation and the eyes were white and quiet. There was no evidence of uveitis or secondary glaucoma.

Summary

An unusual association is reported of aniridia and anterior polar cataract in a case of scaphocephaly. Both lenses subsequently dislocated spontaneously into the vitreous.

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Brit. J. Ophthal. (1971) **55**, 644

Use of the Perkins hand-held applanation tonometer in retinal detachment surgery

A. H. CHIGNELL
Moorfields Eye Hospital, City Road, London, E.C.1

The applanation method is generally accepted as being the most accurate for measuring intraocular pressure. Perkins (1965) described a hand-held portable applanation tonometer. Whitty (1969) reported his results using this tonometer: he found that readings with the hand applanator were slightly (1–1·5 mm.Hg) lower than those taken with the Haag-Streit tonometer, and he felt that this may have been caused by a slight defect in technique. There was no difference between the readings taken with the hand applanator when the patients were sitting and lying.

In a list of uses to which the instrument may be put, Whitty mentioned the operating theatre. The purpose of this communication is to describe the indications and technique for its use in retinal detachment surgery. In this study, the battery-powered model (Fig. 1, opposite) was used, and pressures were recorded in over fifty cases.

Indications

(1) AT THE END OF RETINAL DETACHMENT PROCEDURES DURING WHICH SUBRETINAL FLUID HAS BEEN DRAINED

The main danger in this procedure is hypotony. Hawkins and Schepens (1966) stressed the significance of hypotony in the production of choroidal detachments. They also felt that choroidal haemorrhage was more likely to occur if the globe was left hypotonic after drainage of subretinal fluid, particularly in myopic eyes. Schepens (1968) suggested a final pressure of 10–15 mm.Hg.

(2) DURING PROCEDURES IN WHICH SUBRETINAL FLUID IS NOT DRAINED

This technique has been advocated by Lincoff, Bavas, and McLean (1965), who modified the original procedure of Custodis (1953). During the operation there is always a rise in intraocular pressure as the scleral buckle is produced. The main danger of this procedure is occlusion of the central retinal artery. In many cases it is possible to observe the behaviour of the central artery with indirect ophthalmoscopy; sometimes the view of the artery at the disc may be partially or totally obscured by opacities in the media or even by a ballooned detachment of the retina itself. Recordings of the intraocular pressure would be particularly valuable in these cases.

Bailliart (1917), using ophthalmodynamometry, found the average diastolic pressure in the ophthalmic artery to be 47 mm.Hg, and the systolic pressure 78 mm.Hg. Mikuni and Yoneyama (1960) found pressures of 38·7 and 77·1 mm.Hg. Galin, Baras, and Cavero (1969), using a suction-cup technique, found higher values: in their series of 67 cases the lowest pressures were an ophthalmic diastolic pressure of 60 mm.Hg and a systolic pressure of 109 mm.Hg. This patient had a brachial artery pressure of 120/70 mm.Hg.

Smith and Cogan (1959) considered the relationship between brachial artery and ophthalmic artery pressure. In a series of normal subjects, they found the average systolic

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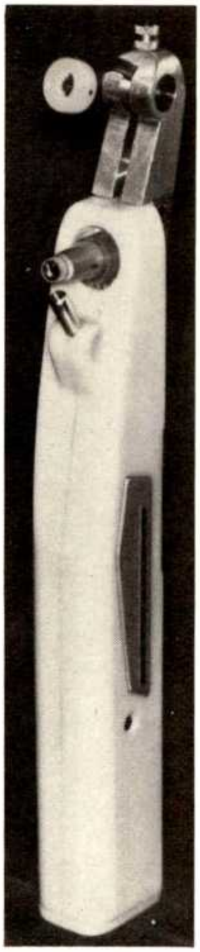
pressure in the ophthalmic artery to be 81·1 per cent. of that in the brachial artery, and the average diastolic pressure to be 72·4 per cent. In patients with frank cerebrovascular disease, the corresponding figures were 73·7 and 64·3 per cent.

These findings suggest that, provided that the systemic diastolic blood pressure does not fall below 75–80 mm. Hg, it is quite safe to raise the intraocular pressure to 30–35 mm. Hg (*i.e.* less than 50 per cent.) even though the central retinal artery cannot be seen. There would seem to be little risk of totally occluding the central retinal artery at this pressure. Exceptions may be cases of retinal detachment in which there is ipsilateral ocular ischaemia (*e.g.* carotid artery stenosis, retinal artery disease, carotico-cavernous fistula), which may result in abnormally low pressures in the ophthalmic artery.

Technique

A small amount of 2 per cent. fluorescein from a freshly opened bottle is placed on the cornea with a glass rod and diluted by a stream of saline. The surgeon then puts on a loose-fitting sterile linen glove and the tonometer is handed to him by an attendant. An applanation prism which has been sterilized in ethylene oxide is inserted into the tonometer by the surgeon. The operating theatre lights are dimmed. It has been found to be most convenient to measure the pressure from the side (Fig. 2). Two separate readings are taken. No part of the instrument other than the sterile applan-



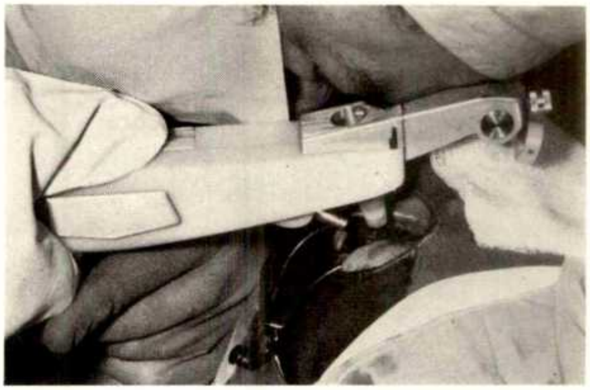


FIG. 2 *Applanator in use during an operation. A sterile linen glove is worn and the eye is approached from the side*

FIG. 1 *Battery-powered Perkins hand-held applanation tonometer*

ation prism touches the operation field. When the readings have been made the attendant takes the instrument and removes the linen glove from the surgeon's hand. With practice the whole procedure can be completed in about 1 minute, and there is little inconvenience.

When subretinal fluid is not drained, pressures are recorded at the beginning of operation, in between and after the tying of the scleral sutures to raise the indent, and at the end of the operation. Pressures are also recorded in the other eye for control purposes. The blood pressure is recorded by the anaesthetist each time the intraocular pressure is measured

DIFFICULTIES ENCOUNTERED

(**1**) Great care must be taken during the operation to see that the cornea remains moist. If it is allowed to dry, the applanation rings become indistinct and accurate readings are difficult to obtain.

(**2**) On one occasion a small unsuspected corneal abrasion was present before tonometry was performed; fluorescein was applied and this resulted in rapid and marked taking up of the stain by the corneal stroma. This slightly impaired the view of the fundus obtained with the indirect ophthalmoscope.

These problems were the only ones encountered in over fifty cases.

Summary

It is considered that accurate measurement of intraocular pressure is essential in retinal detachment procedures involving scleral indentation, either with or without drainage of subretinal fluid. In the former case hypotony is to be avoided and in the latter total occlusion of the central retinal artery is the danger. When subretinal fluid is not drained, applanation tonometry is found to be particularly useful when disc details are partially or totally obscured. In the latter case it is considered that, in the absence of ipsilateral ocular ischaemia and with a diastolic brachial artery pressure of 75–80 mm.Hg, it is safe to raise the intraocular pressure to 30–35 mm.Hg without risk of total occlusion of the central retinal artery. If subretinal fluid is drained, a final pressure of 10–15 mm.Hg has been suggested.

The ease of use of the hand applanator is stressed. Contamination of the operative field is easily avoided. Because of the speed of the procedure there is little inconvenience or unnecessary lengthening of the operation time. In over fifty cases no serious difficulties have been encountered. Care of the cornea during the operation to prevent drying or abrasion is essential.

I wish to thank Prof. E. S. Perkins for his help and advice in preparing this paper and the Department of Audio-Visual Communications, Institute of Ophthalmology, for providing the illustrations. This work was supported in part by a grant from the Clothworkers Company.

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Brit. J. Ophthal. (1971) **55**, 647

Book review

Stereoscopic Atlas of Macular Diseases. A Fundoscopic and Angiographic Presentation. By J. D. M. Gass. 1970. Pp. 232, 498 figs, and 105 stereoscopic views (90 in colour) on 15 reels. Mosby, St. Louis; Kimpton, London. (£21.80)

Donald Gass is certainly one of the very few creative ophthalmologists who are to be found occasionally in every generation. This book brings together in one volume most of the modern ideas on macular disease, many of which originated in his own fertile mind.

He has interpreted fluorescein angiographs and ophthalmological appearances and added his own considerable knowledge of pathology to produce a very logical story of the development of many of the macular diseases which have previously been lumped together as senile macular degeneration, hereditary macular disease, or central serous retinopathy.

The book is divided according to the following twelve chapter headings:

1. Normal macula
2. Choroidal diseases causing localized (disciform) detachment of the retina and pigment epithelium
3. Visual loss caused by wrinkling or folding of the choroid
4. Nonexudative heredodegenerative diseases of the choroid
5. Macular dysfunction secondary to diseases of the pigment epithelium
6. Macular dysfunction caused by retinal vascular diseases
7. Retinal inflammatory diseases affecting the macula
8. Macular dysfunction secondary to traumatic retinopathy
9. Macular dysfunction secondary to neoplastic diseases of the retina
10. Macular dysfunction secondary to non-exudative retinal degenerative diseases
11. Macular dysfunction caused by vitreous abnormalities
12. Serous detachment of the macula secondary to congenital pit of the optic nerve head

The volume is profusely illustrated by fluorescein angiograms with a few pathological photographs, and at the back of the book there is a series of stereoscopic reels with a stereoviewer, which may be used when reading the text. Treatment where suitable is indicated in the text. This book is certainly compulsory reading for all ophthalmologists, not merely for those interested in the retina, but for any one coping with visual problems. The price, unfortunately, is inflationary, but the style in which the book is written makes it a joy to read.

Notes

Retinal Unit, Moorfields Eye Hospital, City Road, London

Consultants' Course, November 24 to 26, 1971

The Consultants' course in 1971 has been extended to occupy 3 days. The first morning is intended as a basic refresher course in the management of retinal detachments. Subsequent sessions will be devoted to more detailed consideration of retinal work, including malignancy, diabetes, macular disease, genetic aspects, and vascular retinopathy. A review of the detachment procedures of this Unit will be given under the headings of Primary Detachments, Prophylaxis, Re-operations, and von Hippel-Landau disease. A demonstration of an Argon Laser is being planned.

The course is based at Moorfields Annexe, Highgate, on Wednesday, and at Moorfields, City Road, on Thursday and Friday. As usual there will be a visit to Kenwood, where a tour of the House and tea will be followed by a discussion of clinical problems. Entertainments have also been planned for Wednesday and Thursday evenings.

The conference fee of £21.00 includes coffee, lunch, tea, and dinner on Wednesday and Thursday, and coffee, lunch and tea on Friday. Transport will be arranged to take participants to and from the President Hotel, Russell Square, W.C.1 (01-837 8844). Accommodation, if desired, should be booked early by personal application to the Hotel.

Consultants, who may nominate a deputy if they wish, should apply to Lorimer Fison Esq., F.R.C.S., 104 Harley Street, London W1N 1AF, enclosing a cheque made payable to Retinal Unit Symposium. The full programme will be sent in acknowledgement. Early application is important as numbers have to be limited.

Paediatric Ophthalmology

Beirut, December 3 *and* 4, 1971

A Post-Graduate Course on Paediatric Ophthalmology will be held at the American University Medical Centre, Beirut, Lebanon, on December 3 and 4, 1971.

Intraocular Implant Club

Budapest, April 22, 1971

The Second Meeting of the Intraocular Implant Club will be held in Budapest at the conclusion of the European Ophthalmological Congress, on Saturday April 22, 1972. The morning session will be devoted to intracameral lens implants and the afternoon to intracorneal prostheses. Short opening papers will be read by members of the Club. Any ophthalmologist who wishes to attend will be very welcome and should write without delay to the Secretary:
Mr. Peter Choyce, MS, FRCS,
45 Wimpole Street, London, WIM 7DG

First International Surgical Eye Symposium

Bologna, April 23 *to* 27, 1972

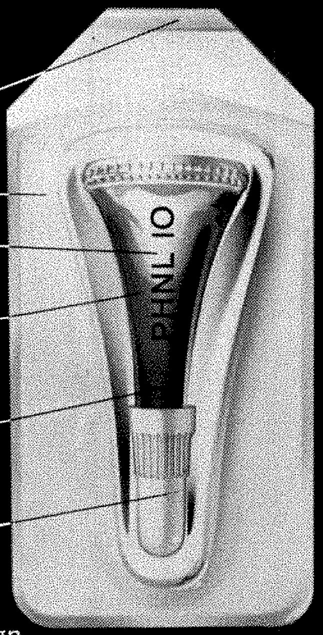
The first International Surgical Eye Symposium will be held in Bologna, Italy, on April 23 to 27, 1972. The subjects will be the management of the anterior chamber angle for glaucoma, congenital and senile cataracts, corneal lesions, prosthokeratoplasties, and plastic surgery of the lids and orbit. Operative sessions will be televised.

Papers related to the above subjects and to recent advances in orbitography, ultrasonography, fluorescein angiography, etc., will be presented. Registration fee U.S. $ 100. Information may be obtained from the Clinica Oculistica, Università di Bologna, Via Massarenti 9, Bologna, Italy.

V Afro-Asian Congress of Ophthalmology

Tokyo, July 9 *to* 12, 1972

Those interested should write to the Secretary-General, Prof. A. Nakajima, The Japanese Organizing Committee for the 5th Afro-Asian Congress of Ophthalmology, c/o Department of Ophthalmology, Juntendo University, Hongo, Bunkyo-ku, Tokyo, Japan.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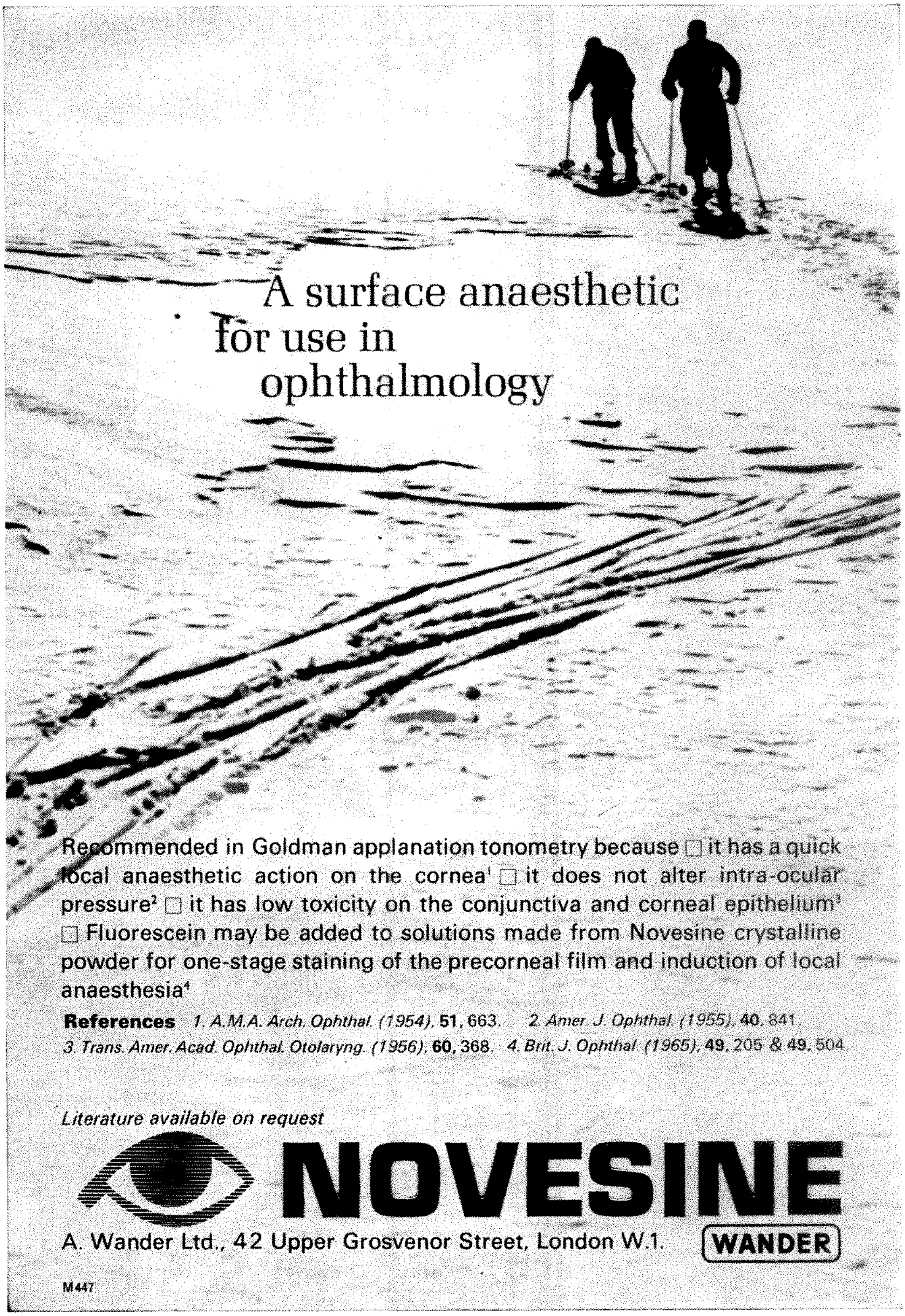

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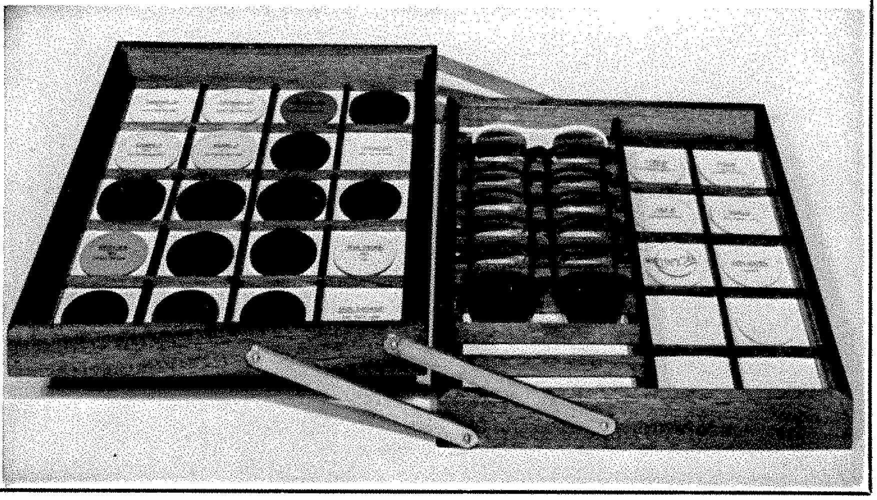

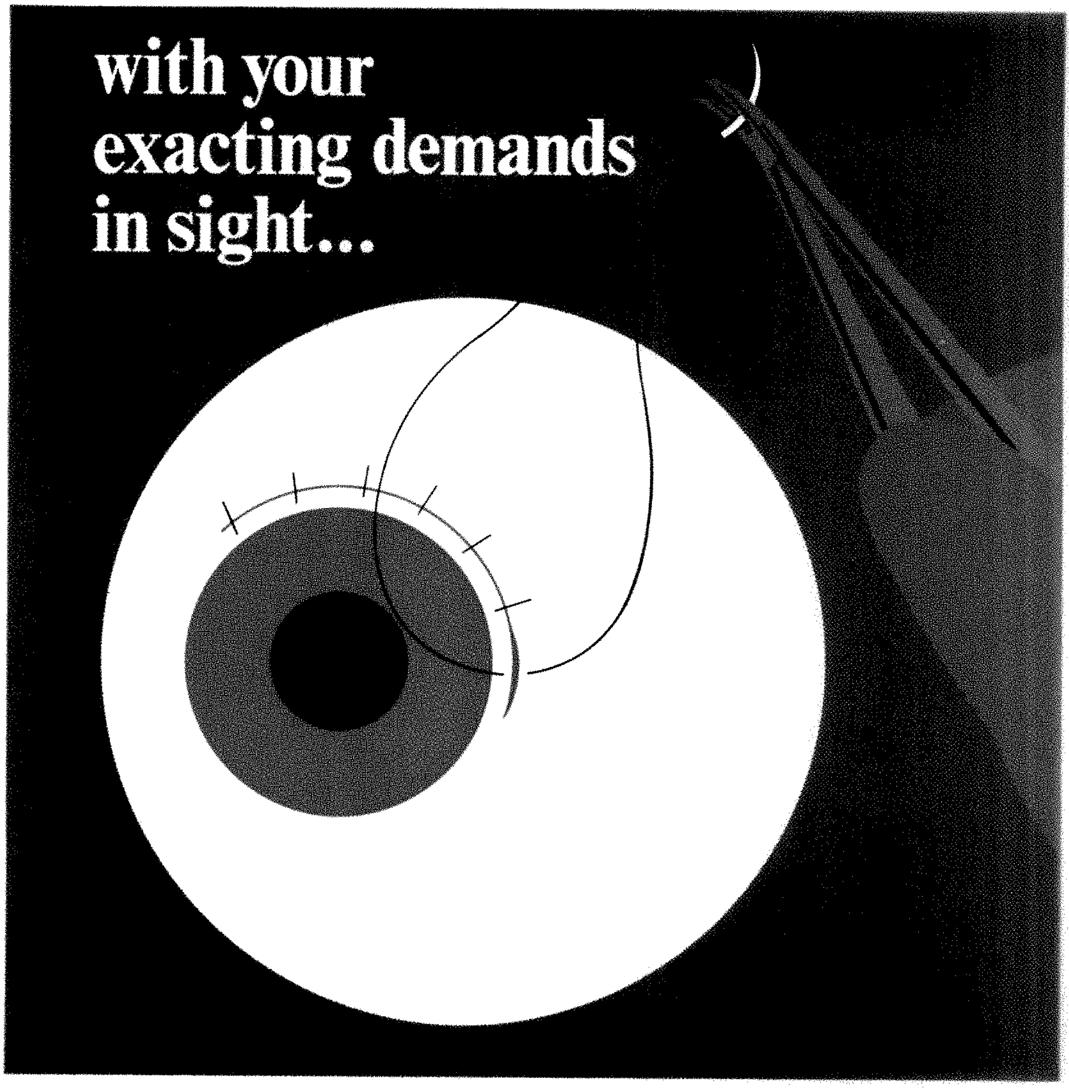

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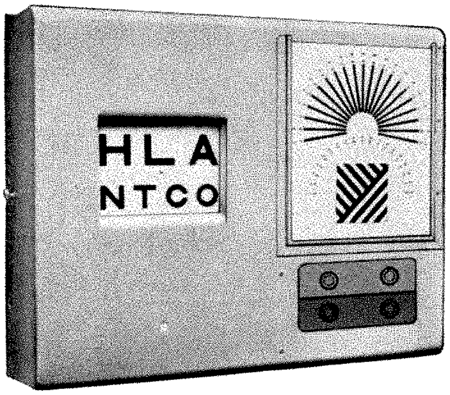

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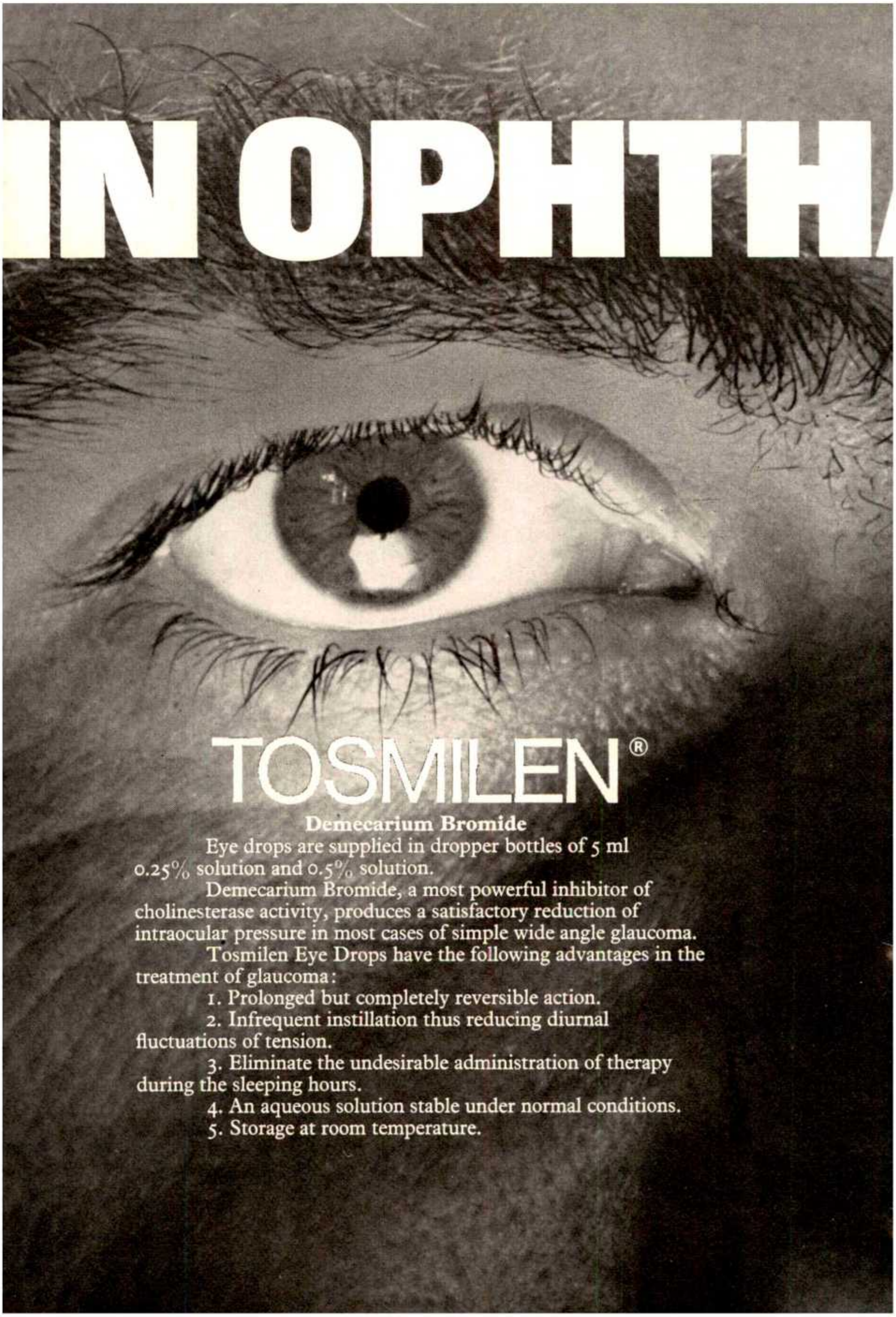

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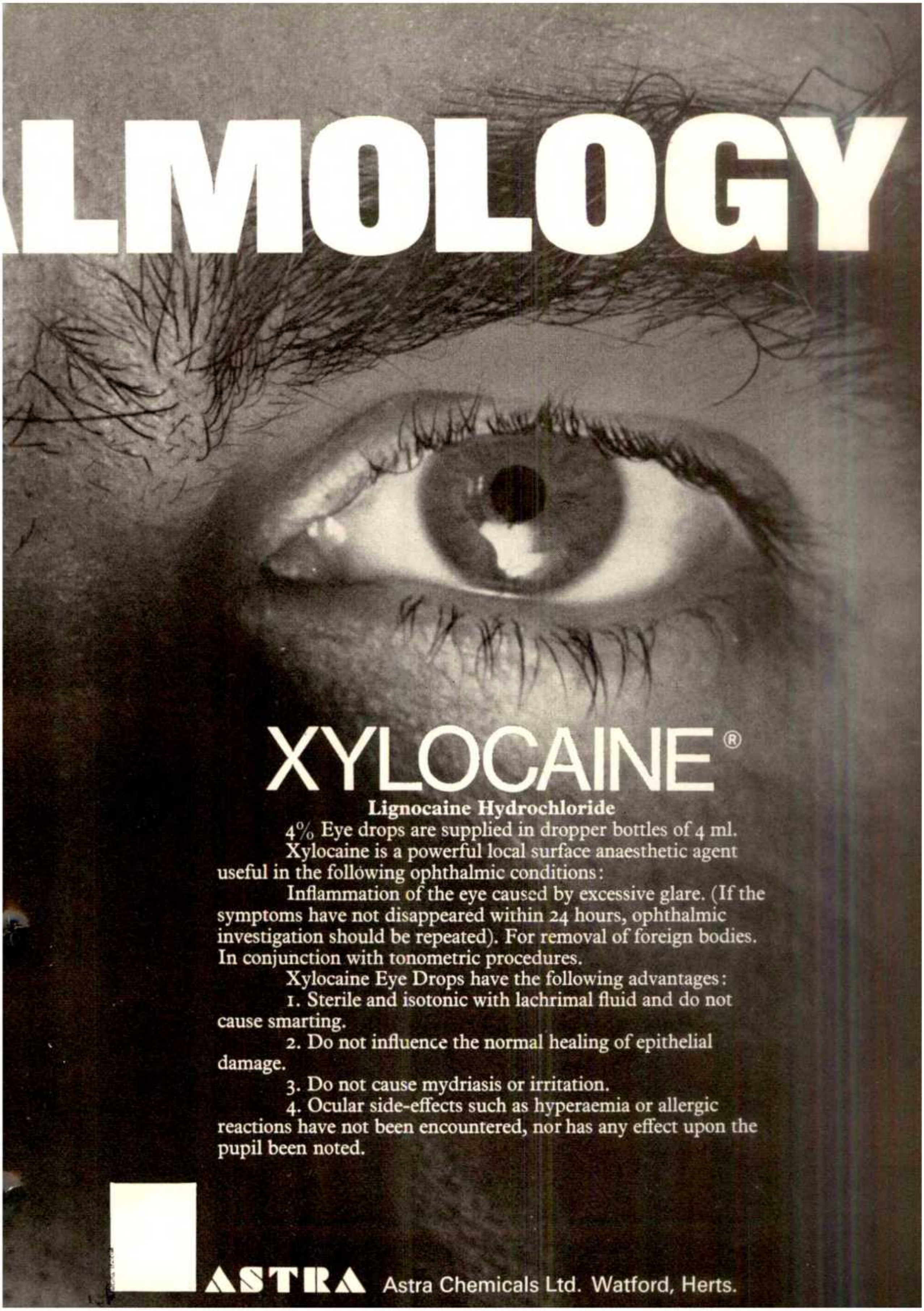

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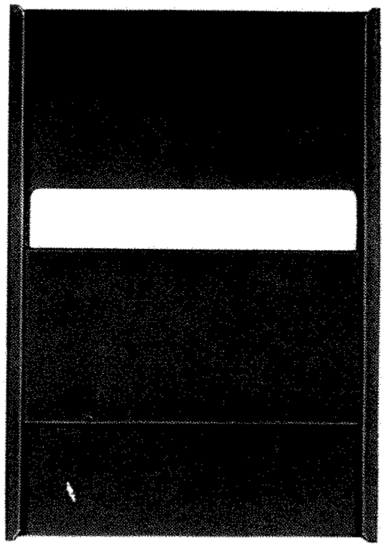

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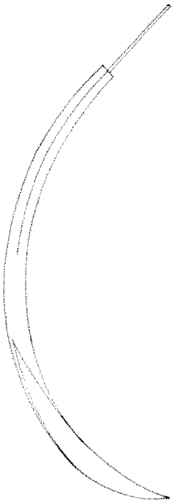

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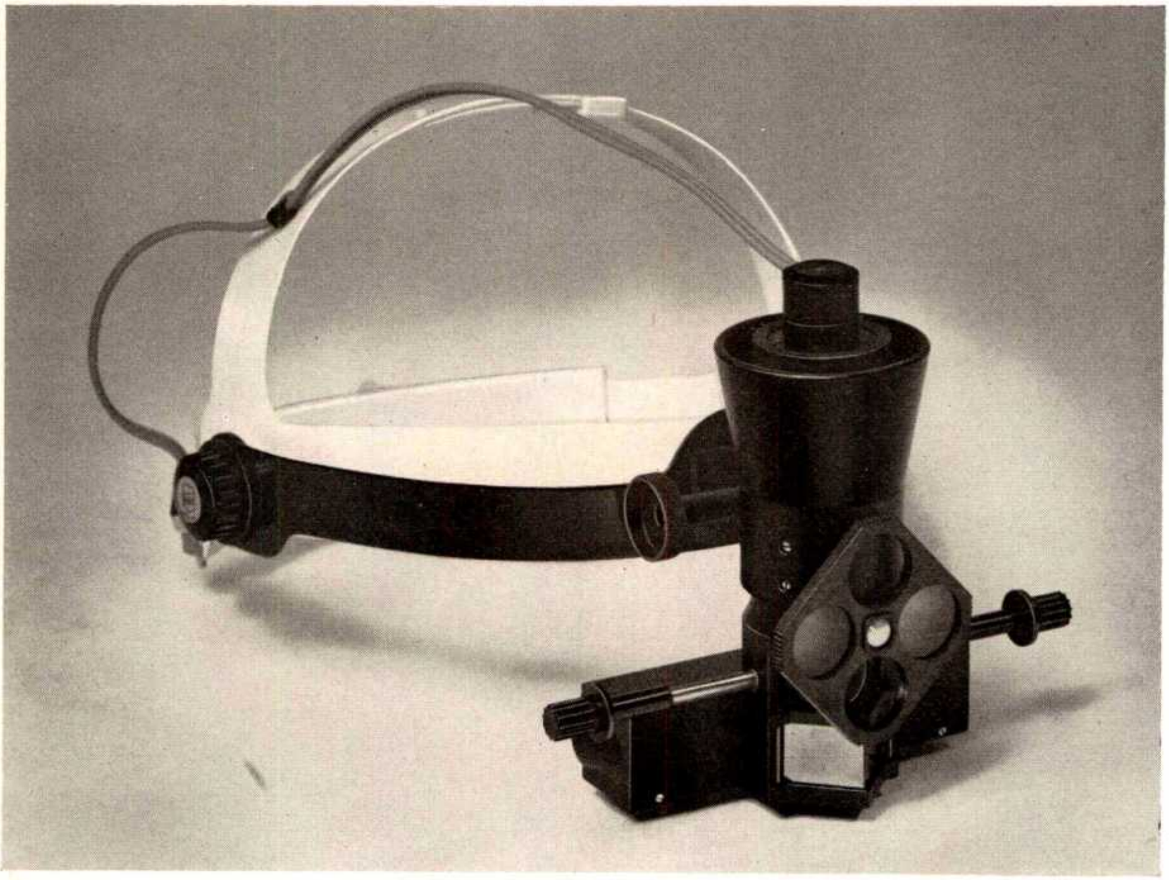

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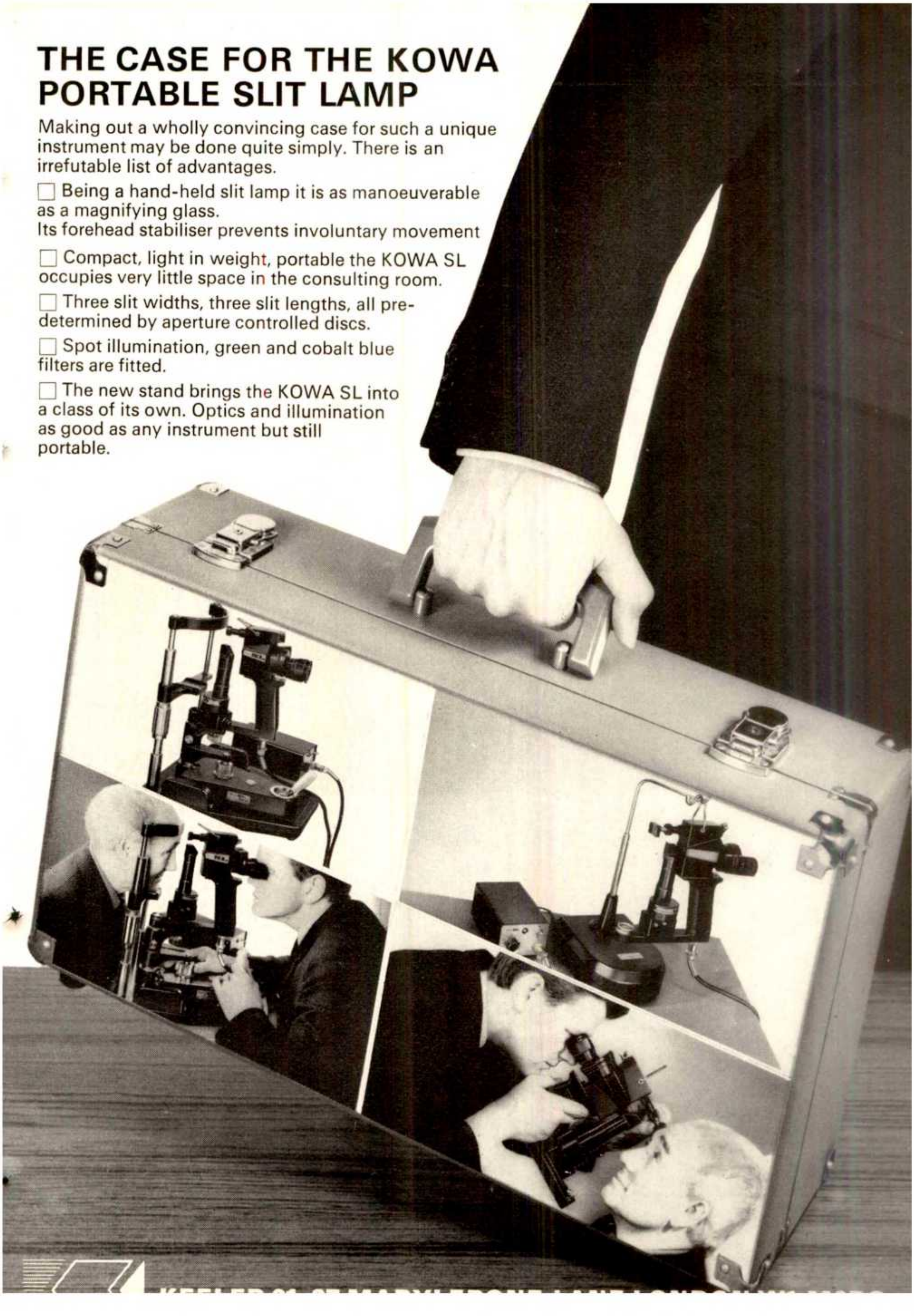

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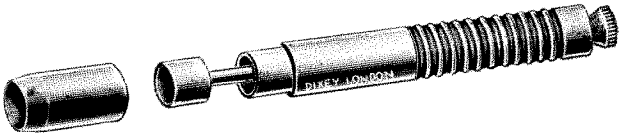

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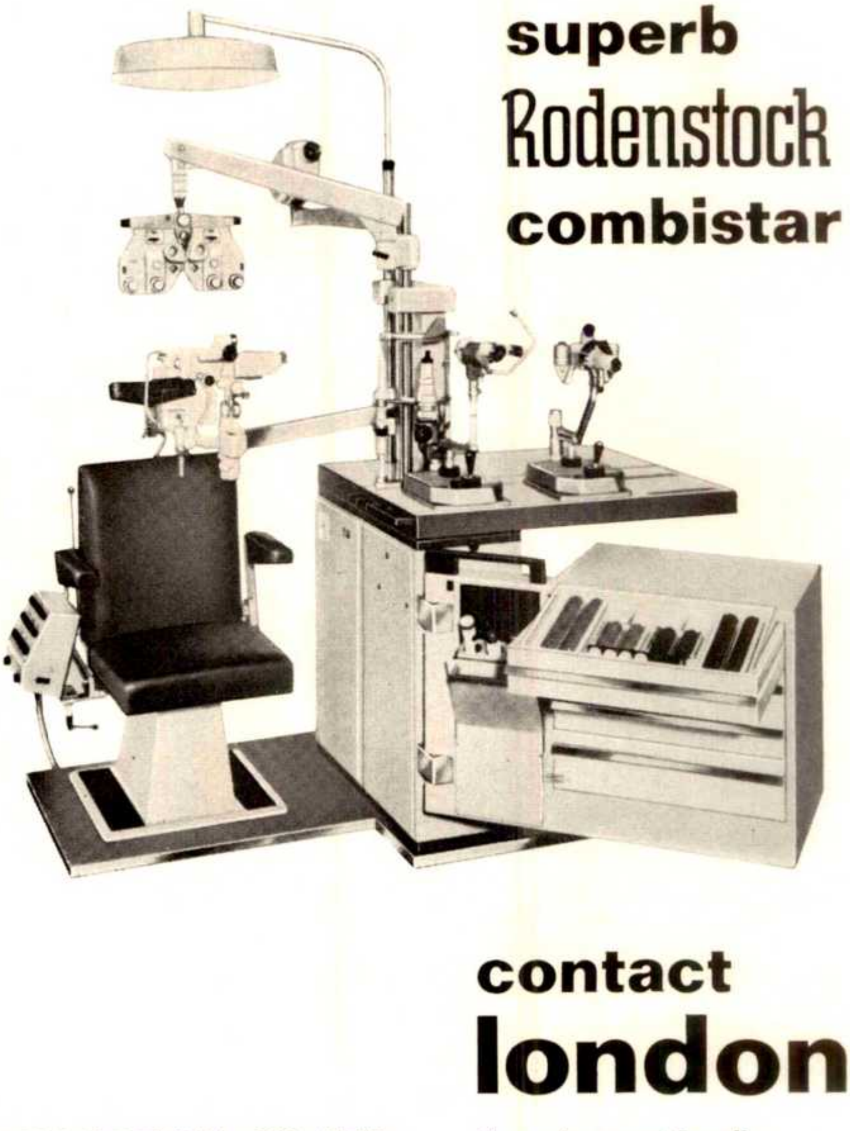

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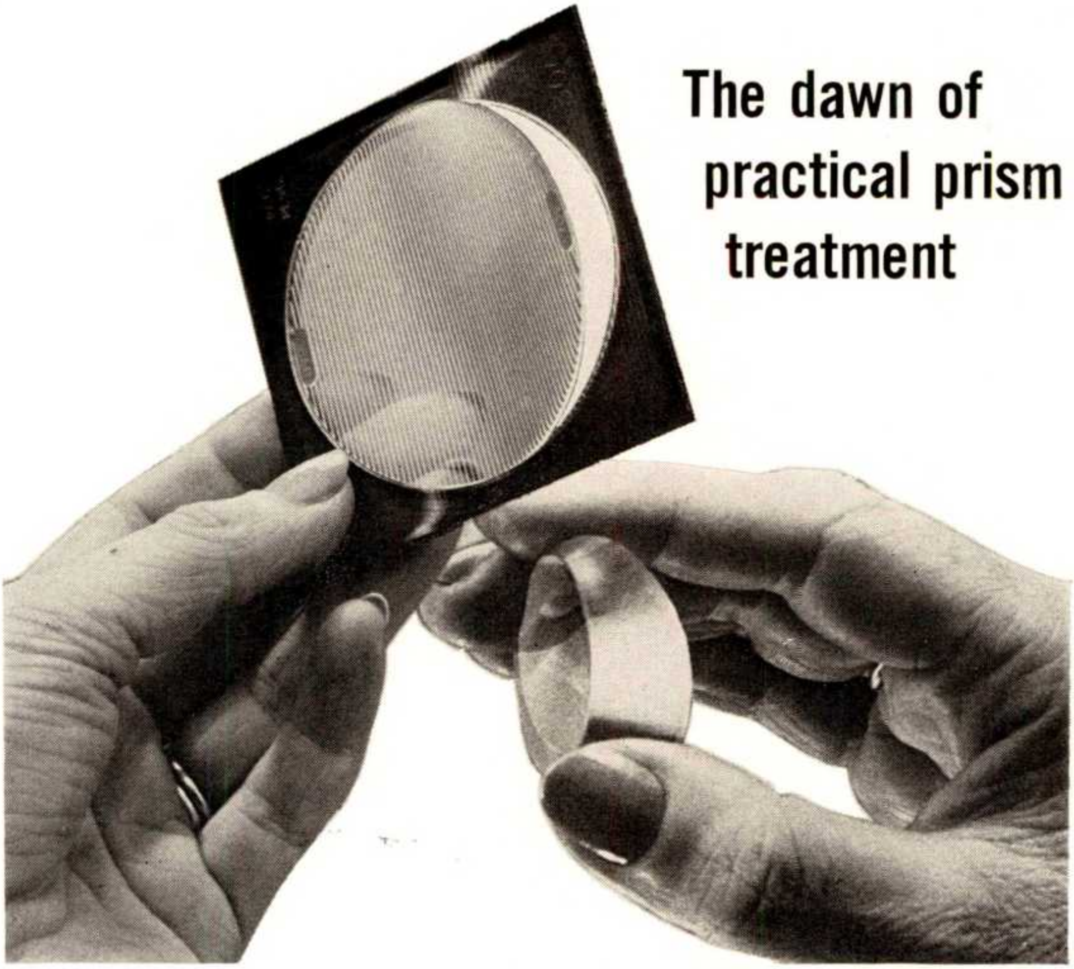

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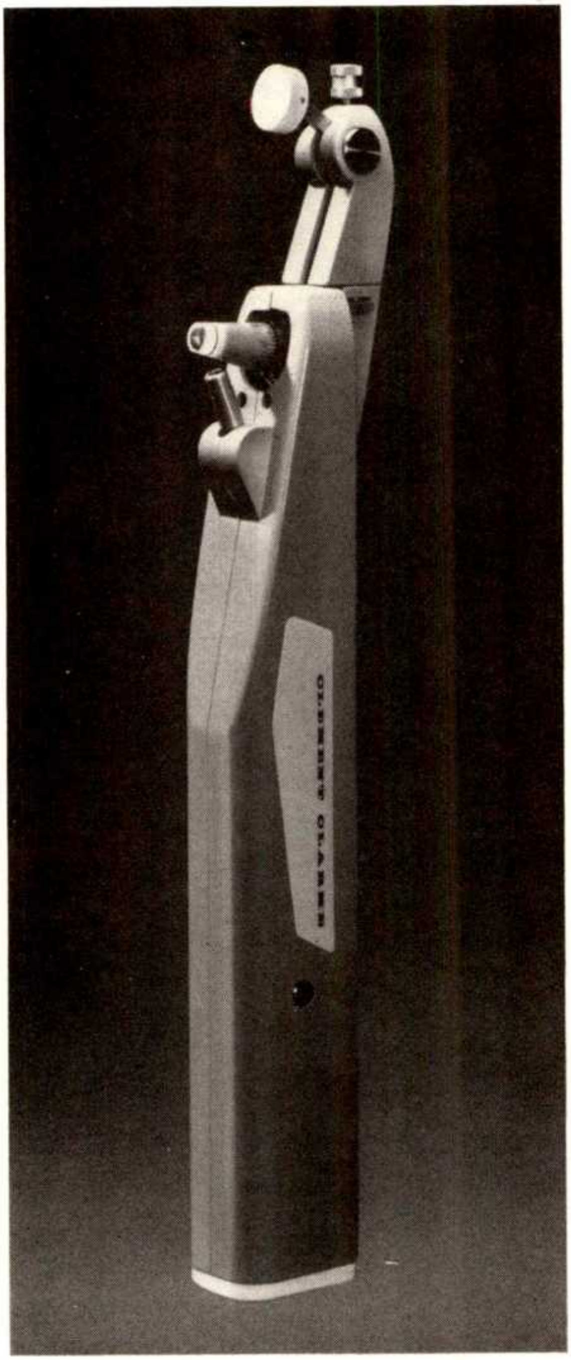

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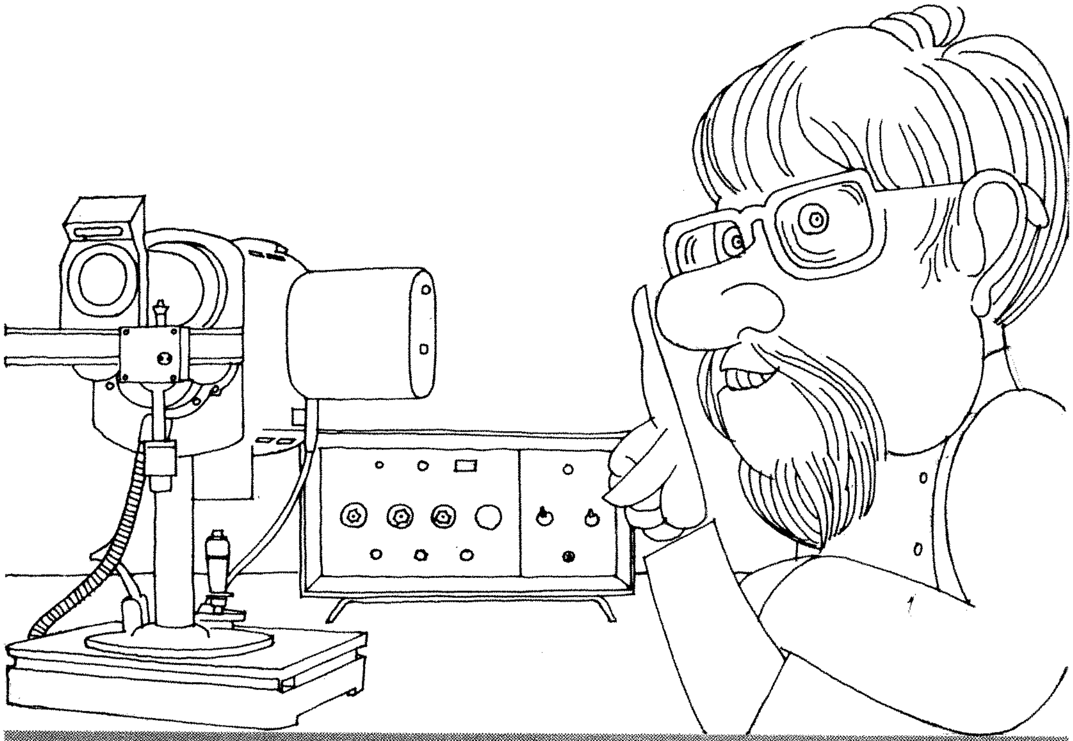

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Communications

Ophthalmic arterial and venous pressures

Effects of acute intracranial hypertension

SOHAN SINGH HAYREH* AND JOHN EDWARDS

From the Department of Experimental Ophthalmology, Institute of Ophthalmology, University of London

Duke-Elder (1926) rightly pointed out that "There is no question in the whole of ophthalmology more important and fundamental than the vascular pressures of the eye". The ophthalmic artery pressure (OAP) has been measured almost invariably by ophthalmodynamometry or other methods based on the same principle, and the results obtained have shown very wide variation (Duke-Elder, 1926; Koch, 1945). Because this has led to much confusion on the subject, and more reliable estimates of the OAP are desirable, direct cannulation of the ophthalmic artery has been used to measure the OAP in rhesus monkeys. The OAP was correlated with the systemic arterial blood pressure (BP) recorded from the aorta, in order to determine whether a significantly close relationship existed between the two arterial pressures, and whether the OAP could be deduced from the BP. In fact, a very close correlation was found, indicating that it is possible to deduce the OAP from the BP by the formula computed in the present study.

The effects of intracranial hypertension on the ophthalmic arterial and venous pressures, and their significance, have been the subject of considerable controversy, especially the role played by raised ophthalmic venous pressure in the pathogenesis of oedema of the optic disc and various types of haemorrhage (pre-retinal, retinal, from the optic nerve and its sheath, and orbital).

The aim of the present study was to investigate the following:

(*i*) The normal ophthalmic arterial and venous pressures.

(*ii*) The correlation of the OAP with the BP, and of the ophthalmic vein pressure (OVP) with the pressure in the intracranial venous sinuses.

(*iii*) The effects of acute intracranial hypertension on these pressures.

(*iv*) In intracranial hypertension, the correlation of change in the ophthalmic arterial and venous pressures with changes in the systemic arterial and venous pressures and the pressure in the intracranial venous sinuses.

(*v*) The effects of acute intracranial hypertension on the fundus of the eye.

In this study, the various pressures were recorded in rhesus monkeys after direct cannulation of the ophthalmic artery, superior ophthalmic vein, abdominal aorta (*via* the femoral artery), internal jugular vein, and superior sagittal sinus. This investigation formed a part of studies on the pathogenesis of oedema of the optic disc in cases of raised intracranial pressure (Hayreh, 1964a, 1965a, 1968).

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* This work was carried out during the tenure of a Beit Memorial Research Fellowship by S.S.H.

Material and methods

This study was carried out in 27 healthy adult rhesus monkeys, weighing between 4 and 8 kg.

They were anaesthetized with intraperitoneal nembutal, 40 mg./kg. body weight, and placed on an electrically warmed animal operating table. Atropine 1 per cent. and phenylephrine 10 per cent. were instilled into each eye to dilate the pupil and the lids were then sutured together to preserve corneal transparency, so that the fundus could be examined at the end of the experiment for any changes.

With the aid of a Zeiss operating microscope the ophthalmic artery and vein were exposed for cannulation at the right supraorbital margin. The superior sagittal sinus was exposed at the vertex, the right internal jugular vein in the neck at about the level of the thyroid cartilage, and the femoral artery and vein just below the inguinal ligament. The vessels were then cannulated in the following order:

(1) *Femoral vein*

This was cannulated in order to inject 5000 i.u. heparin to minimize clotting of the cannulae, and subsequently to administer maintenance doses of nembutal.

(2) *Femoral artery*

1 mm. nylon tubing was inserted as far as the abdominal aorta.

(3) *Internal jugular vein*

A glass T-cannula was used. Each arm of the T carried a soft PVC tube about 2 cm. long and with a 1·5 mm. bore, to prevent the collapse of the wall of the vein where it had been exposed and had lost the support of the surrounding tissue and to maintain the flow of blood to the heart. The vein on the right side was used because it is in direct line with the superior vena cava and right atrium.

(4) *Ophthalmic vein*

0·5 mm. nylon tubing was pushed in for about 2 cm. down the intraorbital section of the vessel.

(5) *Ophthalmic artery*

0·2 mm. nylon tubing was inserted for 0·5 to 1 cm. into the intraorbital section.

(6) *Superior sagittal sinus*

1 mm. nylon tubing was introduced through a small incision in the superficial wall, and pushed in for 4 to 5 cm.

(7) The animal was turned over to lie on its left side and a short-bevel No. II serum needle was introduced into the *cisterna magna* (*cerebello-medullary cistern*) to enable the cerebrospinal fluid pressure (CSFP) to be recorded and elevated.

The cannulae were filled with normal saline and connected to six pressure transducers, the amplified outputs of which were fed to six mirror galvanometers in an ultra-violet recorder, using 12 in. paper.

The pulse rate was measured in seventeen animals by recording the aortic pulse at a high paper speed on another recorder at frequent intervals throughout the experiment.

The initial pressures were recorded first, and a tap connecting a saline-filled reservoir to the CSFP transducer was then opened so that the pressure could be elevated to any desired level by raising the reservoir. The pressure was raised initially to 10 mm.Hg and subsequently increased in steps of 5 mm.Hg about every 5 minutes. The maximum elevation depended upon the response of the animal, so that in some experiments the CSFP did not reach the planned level of 50 mm.Hg or more because the monkey showed signs of distress or collapsed. In fifteen experiments the pressure was raised to 50 mm.Hg, in four to 45, in three to 40, in one to 35, in one to 55, in two to 60, and in one to 70 mm.Hg.

In 22 animals the CSFP was raised above normal for periods varying betewen 45 and 92 minutes, while in the remaining five experiments the time varied between 36 and 120 minutes. The total duration of the elevation of pressure in any particular experiment generally depended on how long the maximum pressure could be tolerated by the animal.

After this, the reservoir was lowered rapidly to zero to record the effect of sudden decompression after an acute intracranial hypertension. Most of the monkeys collapsed immediately or shortly after this procedure. The fundus was examined at the end of the experiment for evidence of any changes.

Results

The responses of the rhesus monkeys to the acutely raised CSFP varied widely. A majority, however, showed a significant degree of similarity. The arterial responses tended to fall into three phases:

(1) *Initial* The CSFP was raised from normal to 15 mm.Hg.

(2) *Middle* The CSFP was raised from 15 to 30–40 mm.Hg.

(3) *Final* The CSFP was raised from 30–40 mm.Hg up to a level which depended on the animal's tolerance of the high pressure.

The effects of the sudden fall in the CSFP are presented separately.

A detailed account of the effects on the systemic arterial blood pressure (BP), pulse rate, superior sagittal sinus pressure (SSP), and internal jugular vein pressure (JVP) are reported elsewhere (Hayreh and Edwards, 1971).

From the continuous recordings in the various animals, the levels of the various pressures and the pulse rate were estimated at the normal CSFP and at each step just before the pressure was raised to the next level, *i.e.* 10, 15, 20 mm.Hg and so on. The data thus collected have been subjected to detailed statistical analysis. Before tests for significance of the differences between the various pressures at the various levels of the CSFP were done, the Friedman two-way analysis of variance was carried out to determine the overall significance of the data.

EFFECTS OF ACUTE INTRACRANIAL HYPERTENSION

Systemic arterial BP

These results have been reported in detail elsewhere (Hayreh and Edwards, 1971). The normal systolic and diastolic BP are given in Table I.

Table I *Normal pressures in Rhesus monkeys*

Pressure (mm.Hg)		*Mean and standard deviation*
Systemic blood	Systolic	132·2 ± 13·4
	Diastolic	71·3 ± 14·1
Ophthalmic artery	Systolic	93·0 ± 15·0
	Diastolic	70·8 ± 10·7
Ophthalmic vein		3·94 ± 1·35
Superior sagittal sinus		3·93 ± 1·53

The variations in BP caused by the rise in CSFP are summarized in Table II. Fig. 1 shows the mean systolic and diastolic blood pressures with standard deviations at different levels of the raised CSFP.

Table II *Variations in systolic and diastolic pressure caused by raised cerebrospinal fluid pressure*

Phase of CSFP		*Initial*		*Middle*		*Final*	
BP		*Systolic*	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*
Variation in BP (mm.Hg)	Mean	−7·31	+1·12	+43·43	+18·91	−26·47	−28·94
	SD	37·22	27·20	63·05	30·02	59·39	26·54

+ = rise in blood pressure; − = fall in blood pressure; SD = standard deviation

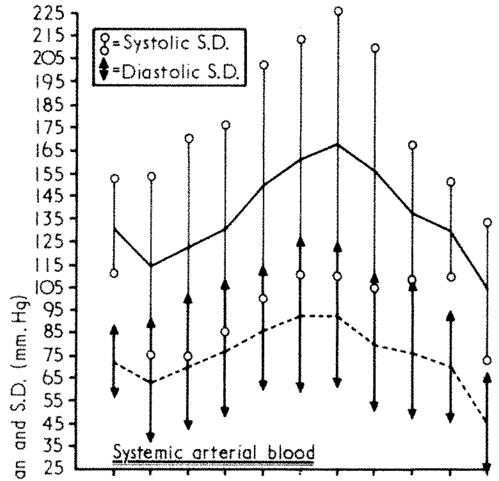


FIG. 1 *Mean systolic and diastolic systemic arterial blood pressures with standard deviations at different levels of raised cerebrospinal fluid pressure*

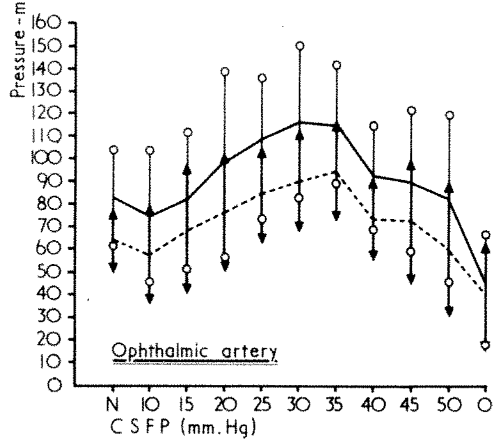


FIG. 2 *Mean systolic and diastolic ophthalmic artery pressures with standard deviations at different levels of raised cerebrospinal fluid pressure*

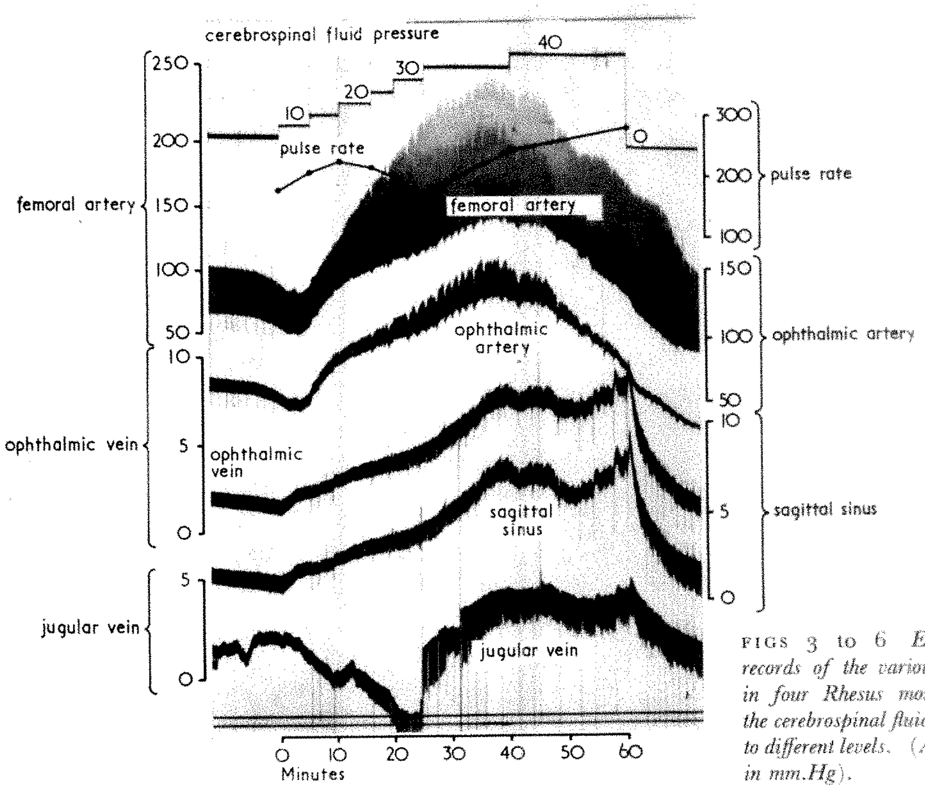
Ophthalmic artery pressure

The normal OAP was 93/71 mm.Hg (Table I). Fig. 2 shows the mean systolic and diastolic OAP with standard deviations at different levels of the raised CSFP.

The correlation coefficient of the OAP (systolic and diastolic) with BP was calculated in the eight animals in which a satisfactory systolic and diastolic OAP was recorded (Figs 3, 4, 5), and the results (Table III) show a significant correlation (at the 0·01 level).

Table III *Spearman's rank correlation coefficient* (*r*) *between ophthalmic artery pressure and blood pressure and their signıficances*

Phase of CSFP	*Normal*		*Initial*		*Middle*		*Final*	
BP	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*
r	0·99	0·98	0·99	0·99	0·82	0·98	0·81	0·99
Significance	0·01	0·01	0·01	0·01	0·05	0·01	0·05	0·01



FIGS 3 to 6 *Experimental records of the various responses in four Rhesus monkeys when the cerebrospinal fluid was raised to different levels.* (*All pressures in mm.Hg*).

Regression equations were computed to calculate the OAP from the BP in normal animals and during the various phases of the rise in CSFP.

(*a*) *Normal animals*

Systolic OAP = 0·80 × systolic BP − 8·63 mm.Hg

Diastolic OAP = 0·80 × diastolic BP + 6·95 mm.Hg

The standard error of the estimate (corrected for small sample) for systolic and diastolic OAP was 3·8 and 3·4 mm.Hg respectively.

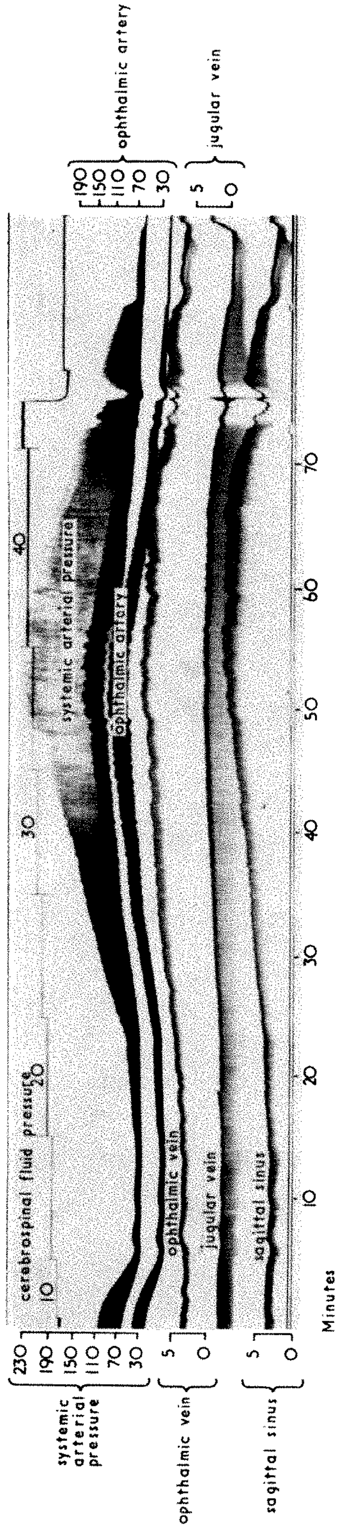
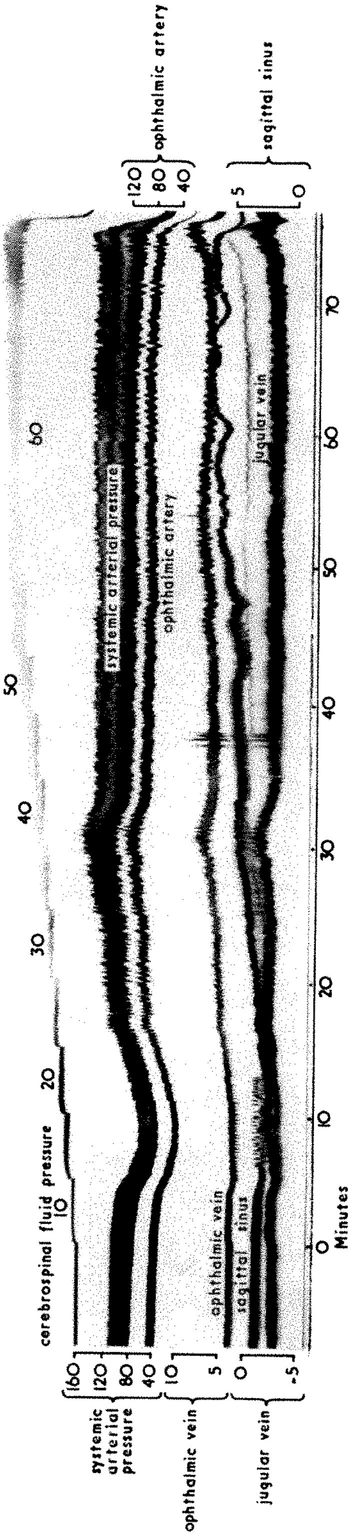

systemic arterial pressure
230
190
150
110
70
30
ophthalmic vein
5
0
sagittal sinus
5
0
Minutes
10
20
30
40
50
60
70
cerebrospinal fluid pressure
10
20
30
40
systemic arterial pressure
ophthalmic artery
ophthalmic vein
jugular vein
sagittal sinus
ophthalmic artery
190
150
110
70
30
jugular vein
5
0

FIG 4


systemic arterial pressure
160
120
80
40
ophthalmic vein
10
5
jugular vein
0
-5
cerebrospinal fluid pressure
10
20
30
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50
60
systemic arterial pressure
ophthalmic artery
ophthalmic vein
sagittal sinus
jugular vein
Minutes
0
10
20
30
40
50
60
70
ophthalmic artery
120
80
40
sagittal sinus
5
0

FIG 5

(*b*) *Initial phase of raised CSFP:*
Systolic OAP $= 0{\cdot}75 \times$ systolic BP $-3{\cdot}6$ mm.Hg
Diastolic OAP $= 0{\cdot}86 \times$ diastolic BP $+2{\cdot}94$ mm.Hg

(*c*) *Middle phase of raised CSFP:*
Systolic OAP $= 0{\cdot}43 \times$ systolic BP $+41{\cdot}6$ mm.Hg
Diastolic OAP $= 0{\cdot}80 \times$ diastolic BP $+12{\cdot}5$ mm.Hg

(*d*) *Final phase of raised CSFP:*
Systolic OAP $= 0{\cdot}88 \times$ systolic BP $-40{\cdot}6$ mm.Hg
Diastolic OAP $= 0{\cdot}86 \times$ diastolic BP $+5{\cdot}5$ mm.Hg

A calculation of the ratio between the OAP and BP from these formulae reveals that during the final phase, the ratio between the two systolic pressures fell to about 47 per cent. from the 70 per cent. that obtained during the earlier phases and in normal animals. Thus the systolic OAP is relatively much lower than the systolic BP during the final phase, but the diastolic OAP and BP show no such disparity.

In eleven other animals, the amplitude of pulsation of the OAP on the record was too small to enable the systolic and diastolic values to be measured separately (Fig. 6). In these cases the pressure recorded was considered to be the mean of the systolic and diastolic OAP. The responses of the OAP in this group were similar to those of the diastolic OAP in the eight animals with satisfactory systolic and diastolic recordings.

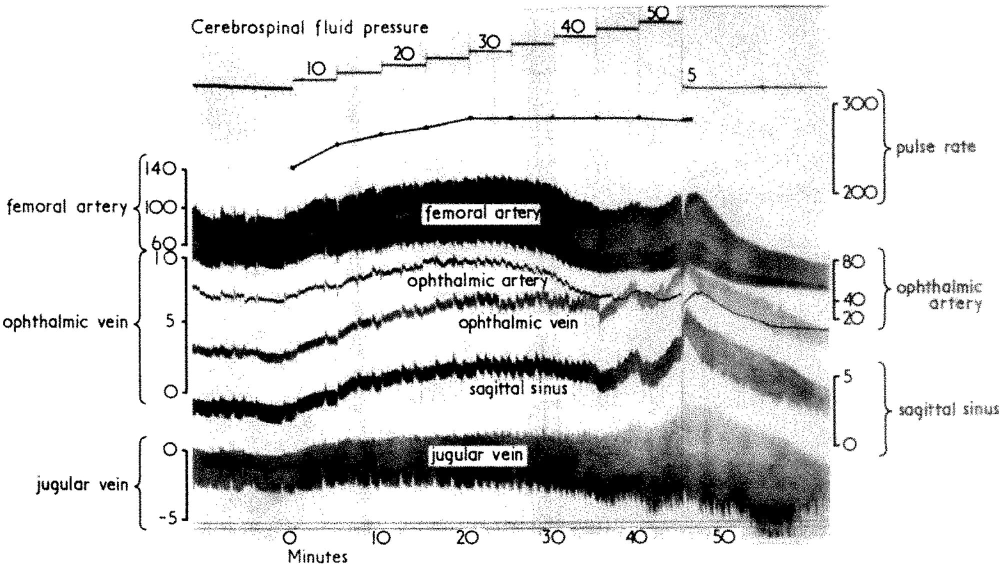

FIG 6

Ophthalmic vein pressure (OVP)

The normal OVP was 3·94 ± 1·35 mm.Hg (Table I). The mean OVP with standard deviations at various levels of CSFP is shown in Fig. 7 (overleaf). There was a significant difference between the spread of results at the beginning and at the end of the raised CSFP.

The correlation coefficient (r) between the OVP and the CSFP mostly varied between 0·80 and 1 (Table IV, overleaf) which is significant at the 0·01 level.

The correlation coefficient between the rise in OVP and the time taken by the CSFP to reach its highest value was equal to 0·21, which is statistically not significant.

Table IV *Spearman's rank correlation coefficient (r) between ophthalmic vein pressure and cerebrospinal fluid pressure*

r	1·0	0·99	0·98	0·97	0·96	0·94	0·93	0·92	0·90	0·89	0·87	0·80	0·60	0·46
No. of animals	1	7	2	2	4	3	1	1	1	1	1	2	1	1
Significance	Present at 0·01 level												None	

The correlation between the OAP (both systolic and diastolic) and OVP is shown in Table V. Although the correlations are positive and substantial, we failed to detect a significant association between the OVP and OAP.

Table V *Spearman's rank correlation coefficient (r) between ophthalmic vein pressure and ophthalmic artery pressure during various phases of rise in cerebrospinal fluid pressure*

Phases of CSFP	*Normal*		*Initial*		*Middle*		*Final*	
OAP	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*
r	0·58	0·60	0·58	0·55	0·69	0·67	0·35	0·21
Significance	None	None	None	None	None	None	None	None

The correlation coefficient between the OVP and SSP (Table VI) was significant at the 0·01 level both in normal animals and in those with a raised CSFP.

Table VI *Spearman's rank correlation coefficient (r) between ophthalmic vein pressure and superior sagittal sinus pressure during various phases of rise in cerebrospinal fluid pressure*

Phases of CSFP	*Normal*	*Initial*	*Middle*	*Final*
r	0·48	0·47	0·59	0·57
Significance at 0·01 level	Present	Present	Present	Present

The normal OVP and JVP showed a statistically significant correlation ($r = 0·46$) at the 0·01 level.

Superior sagittal sinus pressure (SSP)

The normal SSP was 3·93 ± 1·53 mm.Hg (Table I). Fig. 8 (opposite) shows the mean and standard deviations of the SSP at different levels of the CSFP.

The correlation coefficient between the SSP and the CSFP was significant at the 0·01 level (Hayreh and Edwards, 1971).

The correlation coefficient between the SSP and the JVP with normal and raised CSFP was significant at the 0·05 level.

EFFECTS OF SUDDENLY LOWERING THE CSFP AFTER ACUTE INTRACRANIAL HYPERTENSION

Table VII (opposite) shows the responses of the BP, OAP, OVP, SSP, and JVP to the sudden lowering of the CSFP after acute intracranial hypertension. The correlation coefficient between the OVP and SSP changes was 0·82, which is significant at 0·01 level.

A correlated "*t*"-test of the difference between the normal OVP level and that after lowering the CSFP was significant at the 0·01 level.

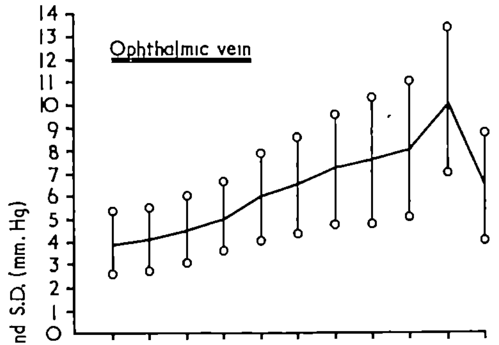

FIG. 7 *Mean ophthalmic vein pressures with standard deviations at different levels of raised cerebrospinal fluid pressure*

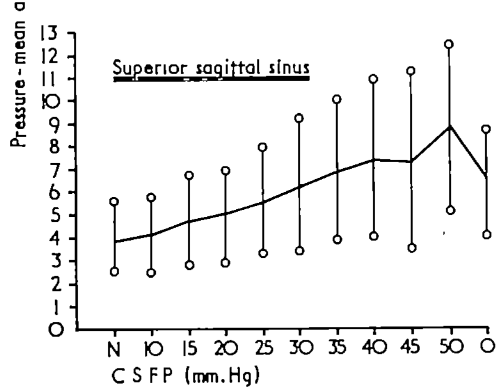

FIG. 8 *Mean superior sagittal sinus pressures with standard deviations at different levels of raised cerebrospinal fluid pressure*

Table VII *Effects of suddenly lowering cerebrospinal fluid pressure after acute intracranial hypertension*

Pressure (mm.Hg)	*BP*		*OAP*		*OVP*	*SSP*	*JVP*
	Systolic	*Diastolic*	*Systolic*	*Diastolic*			
I. Post-lowering level	95·8±32·2	39·1±19·9	42·5±23·0	40·0±25·7	6·4±2·4	6·3±2·3	2·1±2·3
II. Difference in levels between pre- and post-lowering	−36·9±42·7	−21·2±22·2	−23·8±10·4	−16·6±11·0	−3·2±4·5	−2·6±4·1	−0·7±2·4
III. Correlated 't' test for significance of values in Line II	Significant at 0·01 level	Significant at 0·01 level	Significant at 0·01 level	Significant at 0·01 level	Significant at 0·01 level	Significant at 0·05 level	Not Significant

Minus signs in Line II indicate a fall in pressure

It was discovered that if the OVP was less than 7·5 mm.Hg before the CSFP was lowered to zero, it always rose, but if the OVP was 7·5 mm.Hg or more it always fell. A χ^2 test of these changes (with Yates correction for continuity) established that they were significant at the 0·01 level. A significance at the 0·02 level was discovered in similar changes in the SSP.

Discussion

Ophthalmic artery pressure (OAP)

A very close correlation was found in the normal animals between the systemic BP and the OAP. The systolic and diastolic OAP can be estimated from the BP by the formulae given above. This indicates that the systolic OAP is about 71 per cent. of the systolic BP and the diastolic OAP about 87 per cent. of the diastolic BP. These findings are in sharp contrast to those obtained by ophthalmodynamometry (Duke-Elder, 1926; Koch, 1945). Borras and Cabot (1963) recorded the OAP in human beings by cannulation of the supraorbital artery, and in one of their patients, where they had the exact values of the various pressures recorded, the systemic BP was 120/75 mm.Hg and the OAP was 83/65 mm.Hg. The ratios for the systolic and diastolic pressures were 69 and 87 per cent. respectively. These compare very well with those recorded in our series in the normal rhesus monkey.

Duke-Elder (1932) pointed out that, when the column of blood contained in a vessel was partially or completely immobilized, the pressure registered was the lateral pressure at the most proximal arterial branching. The ophthalmic artery is the first major branch of the internal carotid artery. Thus the OAP reflects the internal carotid artery pressure. In rhesus monkeys, the ophthalmic artery gives off large branches during its course through the orbit, the last being the medial palpebral artery (Hayreh, 1964b). We cannulated the ophthalmic artery near the supraorbital margin and the pressure recorded was that of the blood column in the ophthalmic artery distal to the branching of either the ethmoid artery or the medial palpebral artery. Thus, the OAP recorded by this procedure may be somewhat lower than the internal carotid artery pressure, but for all practical purposes we can assume that the OAP is a fairly good index of the internal carotid artery pressure and the various changes in it. Hence the OAP may also be used to determine changes in the cerebral circulation (Hayreh and Edwards, 1971). Since a close correlation exists between the OAP and BP (Table III), it is assumed that the BP is normally a fair index of the ophthalmic and cerebral circulation. This, however, would not apply in cases of stenosis of the carotid system or the ophthalmic artery. There is thus an urgent need for a more accurate means of measuring the OAP than that provided by ophthalmodynamometry.

Effects of raised CSFP on OAP

Hedges (1963) raised the CSFP to 40 mm.Hg in one monkey and did not record any change in the OAP. He concluded that subacute experiments of any duration were not possible with this technique. We have however been able to perform similar experiments in nineteen monkeys in the present series and have found responses in the OAP in all of them.

Responses of the systemic BP to raised CSFP are discussed elsewhere (Hayreh and Edwards, 1971). During the rise in CSFP from normal to 15 mm.Hg, the systemic BP showed a slight fall, particularly in the systolic pressure; it then began to rise with further elevation of the CSFP. In the majority of the animals, it reached its highest level when the CSFP was at 30–40 mm.Hg. After that, any further rise in the CSFP usually led to a fall in the BP (Table II, Fig. 1).

On elevation of the CSFP in the present study, the correlation between the diastolic ophthalmic and systemic blood pressures was well maintained throughout the time that the CSFP was raised (Table III). The correlation of the systolic OAP with the systolic BP was maintained up to about 35 mm.Hg CSFP, but beyond that level the ratio dropped significantly, so that during the final phase the systolic OAP was 47 per cent. of the systolic BP as compared to the normal 71 per cent. This fall in the ratio of the systolic pressures at high levels of the CSFP seems to be due to the "cuffing effect" of the raised CSFP on the intracranial portion of the ophthalmic artery. This cuffing effect would not interfere with the diastolic OAP. The formulae for calculating the OAP from the BP at various levels of the CSFP are given above.

Berens, Smith, and Cornwall (1928), using ophthalmodynamometry in patients with raised intracranial pressure, found a raised pressure in the central retinal artery which was not associated with a rise in the systemic BP. They concluded that there was a selective rise in the OAP in these cases. Bailliart (1923) said the pressure in the retinal arteries always rose in patients with brain tumours and that this was associated with a normal systemic BP (Bailliart, 1954). Huber (1961) also concluded that "in an incipient papilloedema a discordant increase in the pressure in the retinal arteries, provided there is no evidence of a systemic hypertension, may be interpreted as an indication of an increased intracranial pressure." Similarly, Magitot (1922) thought that a raised OAP: BP ratio was of significance in such cases. Streiff and Monnier (1946) and Weigelin (1954), however, showed that such an increase in the OAP: BP ratio was the exception rather than the rule.

Our studies have shown no such selective rise in the OAP in acute intracranial hypertension. The rise in the OAP simply reflects a similar rise in the systemic BP. It may be stressed that all these authors measured the central retinal artery pressure by ophthalmodynamometry; this is an unreliable and erratic means of determining the absolute central retinal artery pressure and not much significance should be attached to it.

A sudden fall in the CSFP always produced a significant fall in the OAP (both systolic and diastolic) which seemed to be secondary to similar changes in the systemic BP. No relationship was discovered between the original and final steady-state OAP, or between the level from which the CSFP fell and the amount of the change in pressure.

Ophthalmic vein pressure (OVP).

Hedges (1963), on cannulation of the superior ophthalmic vein in rhesus monkeys, found the OVP to be approximately 4 mm.Hg. In our series the normal OVP was 3.9 ± 1·3 mm.Hg.

On raising the CSFP to about 40 mm.Hg in nine experiments in rhesus monkeys, Hedges (1963) found a significant rise in the OVP in seven animals (30 mm.Hg in two, 11 in two, and 13, 16, and 24 in the remaining three). The effects of the raised CSFP on the OVP in our series (Fig. 7) are in sharp contrast to the findings of Hedges (1963).

A highly significant correlation was seen between the OVP and CSFP (Table IV): the higher the CSFP the higher the OVP. The time taken by the CSFP to reach its highest level did not significantly influence the OVP.

A correlation between the OVP and OAP (both systolic and diastolic) was looked for (Table V) but no significant relationship between the two was found. This indicates that the OAP does not influence the OVP.

A significant correlation was observed between the OVP and SSP (Table VI): the higher the OVP, the higher the SSP. This seems to us to be an important finding. It is reasonable to assume that the OVP reflects the venous pressure in the cavernous sinus, into which the ophthalmic veins drain. This is because the raised CSFP cannot influence the OVP directly. The correlation discovered between the OVP and the internal jugular vein pressure (JVP) in normal animals does not mean that the OVP is controlled by the general venous pressure in the head and neck, but that it is an indirect reflection of the significant correlation between the SSP and JVP. This is because the superior sagittal sinus and other intracranial venous sinuses drain into the internal jugular vein and the SSP and OVP show a close correlation. The fact that no correlation was discovered between OVP and JVP on elevation of the CSFP supports the concept that OVP and JVP are independent.

The observations indicate that the venous pressures in the cavernous sinus and superior sagittal sinus are related to one another, although no direct communication was found to exist between the two sinuses in the specimens studied by Weinstein and Hedges (1962).

According to Hedges (1963), the orbital venous responses to raised CSFP could be due to:

(1) Interference with venous outflow from the orbit into the cavernous sinus, produced by compression of the wall of the sinus.

(2) The arterial pressor responses.

(3) Possibly on auto-regulatory haemodynamic mechanism in the orbital vascular bed.

Hedges suggested that the initial increase in the OVP was due to the first factor and that the continued and prolonged elevation of the venous pressure was probably due to the third factor, while the second factor was unimportant. We find it difficult to postulate the existence of an auto-regulatory haemodynamic mechanism in the orbital vascular bed, as there is no evidence available to suggest its existence. Since no correlation was seen between the OVP and OAP, the presence of any influence by the OAP on the OVP can be excluded. It must, however, be mentioned that, during the later part of the final phase of the raised CSFP, the OAP usually fell (Fig. 2) while the OVP rose (Fig. 7); this may have been due to the change in the peripheral resistance in the orbital arterioles as part of the generalized vasomotor depression in the body, not limited to the orbital vessels. A fall in peripheral resistance may lead to a fall in the OAP and allow blood at a higher pressure to reach the veins. This may be a contributory factor to the raised OVP in the later stages of the raised CSFP only. Our conclusion is that the primary factor controlling the OVP is the pressure in the cavernous sinus, because a significant correlation exists between the SSP and OVP in the normal animals and throughout the duration of the raised CSFP. There is no reason to assume that the pressure in the various intracranial venous sinuses is not the same.

The raised pressure in the orbital veins, including the central retinal vein, in cases of intracranial hypertension has been postulated as the cause of oedema of the optic disc (papilloedema) and of haemorrhages in the sheath of the optic nerve and pre-retinal haemorrhages. Both these subjects have been discussed at length elsewhere (Hayreh, 1963, 1965a, 1968), and a brief review is given below.

Türck (1853) was the first to suggest that the retinal haemorrhages in cerebral tumours were due to stasis in the cavernous sinus caused by the raised intracranial pressure. A similar view, explaining the pathogenesis of oedema of the optic disc in intracranial tumours, was put forward by von Graefe (1860), according to whom this produced choking of the blood in the retinal veins resulting in oedema of the disc. Heymann (1864), Judeich (1900), Merz (1900), and von Krüdener (1907) considered a rise in pressure in the cavernous sinus to be a factor responsible for oedema of the disc.

Sesemann (1869), Picqué (1888), and Schieck (1910) contradicted this hypothesis on the basis of the existence of extensive anastomoses of the ophthalmic veins with one another and also with the anterior facial vein. The latter communication of the ophthalmic vein would prevent venous stasis in the event of an impediment at the cavernous sinus. In our experiments, as in those of Hedges (1963), the cannulation of the superior ophthalmic vein blocked the communication with the anterior facial vein; thus the rise in the OVP seen in our experiments may represent a higher rise than that seen under normal circumstances. Gurwitsch (1883), after a thorough anatomical examination, concluded that the greater part of the orbital venous blood flowed into the cavernous sinus.

Weigelin (1950), in his haemodynamic theory, has tried to resuscitate the original theory of von Graefe and to rule out the objections to it of Sesemann (1869). According to Weigelin, blood flows from the ophthalmic veins towards the cavernous sinus, but a large part of the drainage of the anterior part of the orbit takes place *via* the anastomotic channels into the facial veins. Normally the difference in pressure between the cavernous sinus and the point where the anastomotic channels leave the ophthalmic vein is very small. Whenever the pressure in the cavernous sinus rises because of intracranial hypertension, blood starts to flow from the sinus towards the ophthalmic vein. The central retinal vein opens into the cavernous sinus directly or through a short branch into the ophthalmic vein. In the event of a rise in pressure in the cavernous sinus, the blood from the central retinal vein cannot flow directly into the cavernous sinus. This leads to a rise in pressure in the central retinal vein, producing oedema of the optic disc.

Kornder (1919) and Hayashi (1955), from their observations in experimental intracranial hypertension in dogs, concluded that raised intracranial pressure produced a generalized rise in venous pressure, leading to engorgement of the retinal veins.

According to Hedges (1963), there is a dramatic rise in pressure in the ophthalmic vein with acute elevation of the intracranial pressure, and the rise is associated with retinal venous engorgement and haemorrhages; the mechanism of this rise in the OVP, as described by him, is discussed above (p. 660). He also found, however, that the SSP fell when the intracranial pressure was raised.

Experimental investigations by Lamach, Claude, and Targowler (*cited by* Lauber, 1935) showed that the blood pressure in the venous sinuses was partly independent of the intracranial pressure. Ryder, Espey, Kristoff, and Evans (1951) observed a fall in pressure in the sigmoid sinus when the intracranial pressure in rhesus monkeys was raised, and they considered the sigmoid sinus pressure to be dependent upon the cardiac output.

The role of raised retinal venous pressure in the causation of oedema of the optic disc has been discussed at length elsewhere (Hayreh 1965a, 1968). It was observed that the raised retinal venous pressure was not the primary factor in the pathogenesis of disc oedema, but was in fact secondary to it (Hayreh, 1965a, 1968, 1969). In the present series of animals with acute intracranial hypertension, oedema of the optic disc was not seen, and the raised OVP in cases of raised intracranial pressure is thus irrelevant to the pathogenesis of disc oedema. The absence of disc oedema in all the monkeys in the present series also indicates that acute intracranial hypertension is not associated with disc changes, and that there is a latent period of many hours, if not days, between the rise in intracranial pressure and the production of oedema of the disc.

The exact mechanism of haemorrhages in the orbit, the optic nerve, the sheath of the optic nerve, and the retina (particularly pre-retinal haemorrhages) in cases of a sudden rise in intracranial pressure, especially in subarachnoid haemorrhages, has been the subject of considerable speculation. Liebrecht (1906), Greear (1943), Walsh and Hedges (1951), Smith, Kearns, and Sayre (1957), Hansen (1958), Ikui and Mimatsu (1961), and many others, have considered these haemorrhages to be secondary to the raised ophthalmic venous pressure produced by the sudden rise in the intracranial pressure.

In the present study, the rise in the OVP, though always seen, was never greater than 12 mm.Hg with a rise of 50 mm.Hg in the CSFP, and on average the rise was about

7 mm.Hg (Fig. 7). The possibility of a patient having an increase in intracranial pressure of more than 50 mm.Hg and remaining alive is remote. Therefore the findings in the present series are applicable clinically. It is extremely unlikely that the extent of the rise in the ophthalmic venous pressure, as indicated by the present study, could produce such haemorrhages. The blood pressure in the normal retinal veins is more than 20 mm. Hg (*i.e.* higher than the intraocular pressure). In cases of partial or complete central retinal vein occlusion (not associated with any arterial ischaemia), no retinal haemorrhages are usually seen in spite of a very high venous pressure (Hayreh, 1965b, 1971). This was further confirmed by the fact that no pre-retinal, retinal, or optic nerve sheath haemorrhages were seen in any of the animals in the present series. Most probably the various ocular and extraocular venous haemorrhages described in cases of subarachnoid haemorrhage are due to the accompanying convulsions. Generalized convulsions of the body would be associated with a sudden tremendously high venous pressure in the head and neck, far greater than that seen with raised intracranial pressure. This sudden rise in venous pressure to extremely high levels could rupture the thin-walled venules and result in widespread haemorrhages in the orbit, the optic nerve and its sheath, and the retina. The absence of haemorrhages in the monkeys of the present series may be due to the absence of convulsions.

A peculiar response of the ophthalmic vein to a sudden drop in the CSFP was discovered, *i.e.* if the OVP was less than 7·5 mm.Hg before the CSFP was lowered to zero, the OVP always rose, but if the OVP was 7·5 or more it always fell. It is not possible to give a satisfactory explanation for this variation. Possibly it is due to the presence or absence of cerebral venous drainage to the cavernous sinus. If the cavernous sinus has no cerebral tributaries, the venous return to it is mainly from the ophthalmic vein and the OVP may fall when the CSFP is lowered. However, if the sinus has large cerebral tributaries, a rise in the CSFP could hamper venous drainage from the cerebral veins and a fall in the CSFP would lead to increased venous drainage and hence to a rise in the pressure in the sinus, reflected in the raised OVP.

Summary

In 27 rhesus monkeys, the normal systemic and ophthalmic arterial and venous pressures and superior sagittal sinus pressure were recorded after cannulation. The effect of acute intracranial hypertension on each was studied. The ophthalmic and systemic arterial pressures showed a close correlation and formulae were computed for deducing the former from the latter. Both rose, with a rise in cerebrospinal fluid pressure up to 30–40 mm. Hg, but further increases in CSFP usually produced arterial decompensation. The ophthalmic venous pressure and superior sagittal sinus pressure showed a significant correlation with each other and with the rise in the CSFP. The role of a raised OVP resulting from a raised CSFP in the pathogenesis of oedema of the optic disc and various ocular and extra-ocular haemorrhages is discussed. Sudden intracranial decompression after hypertension produced a fall in the arterial pressures and rise or fall in the OVP and SSP. The fundus afterwards showed no abnormality.

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Intraepithelial carcinoma ("Bowen's disease") of the cornea

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Pre-invasive carcinoma of the skin epithelium was first described by Bowen (1912) under the name of precancerous dermatosis; 30 years later McGavic (1942) reported five cases of a similar disorder affecting the corneal and limbal epithelium of the eye. Since then many more ocular cases have been recorded. In the belief, however, that a terminology based on the pathology of a lesion is preferable to an eponymous nomenclature, it would seem proper, in describing pre-invasive neoplasia of the epibulbar epithelium, to abandon the commonly applied ascription 'Bowen's disease' in favour of the more explicit term 'intraepithelial squamous cell carcinoma.'

The clinical features of the disorder are characteristically described as those of an ill-defined, slightly elevated, vascularized lesion with a gelatinous appearance, the condition occurring predominantly in elderly patients and in males more often than in females (Reese, 1963). Not infrequently there is a history of previous corneal injury or inflammation. Several reports have stressed the relatively benign behaviour of the majority of such cases regardless of the degree of malignancy indicated by histological appearances (Ash and Wilder, 1942; Ash, 1950; Irvine, 1963).

Though there are at present two reports of the ultrastructure of invasive carcinoma of the corneal epithelium (Tanabe and Tanabe, 1965; Radnot and Lapsis, 1970), the fine structure of preinvasive carcinoma in this situation has not been described. In this combined clinical, histological, and electron microscopical study of such a case, emphasis is placed on the clinical aspects, a detailed analysis of the ultrastructure being provided elsewhere (Tripathi and Garner, 1972).

Case report

CLINICAL FEATURES

An 80-year-old man was first seen in the Corneal Clinic at the Croydon Eye Unit on May 4, 1970. He complained of impaired vision in both eyes of 3 years' duration. Neither he nor his relatives had noticed any other abnormality and his general health was good. The visual acuity with correction was 6/18 in the right and 6/12 in the left, and he was found to have bilateral senile cortical lens opacities. The right cornea showed a flat opalescent cauliflower-shaped lesion extending from the pupillary margin to the limbus between the 12 and 3 o'clock meridians. The lesion was avascular apart from a narrow zone at the limbus and was sharply demarcated from the otherwise normal corneal tissue. Slit-lamp biomicroscopical examination suggested that the lesion was entirely

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confined to the epithelial layer (Fig. 1). The fundi were normal and routine investigations all gave negative results. A provisional diagnosis of intraepithelial carcinoma was made and a partial lamellar keratectomy was performed on July 14. Post-operative progress has been satisfactory but it is proposed to keep the patient under observation.

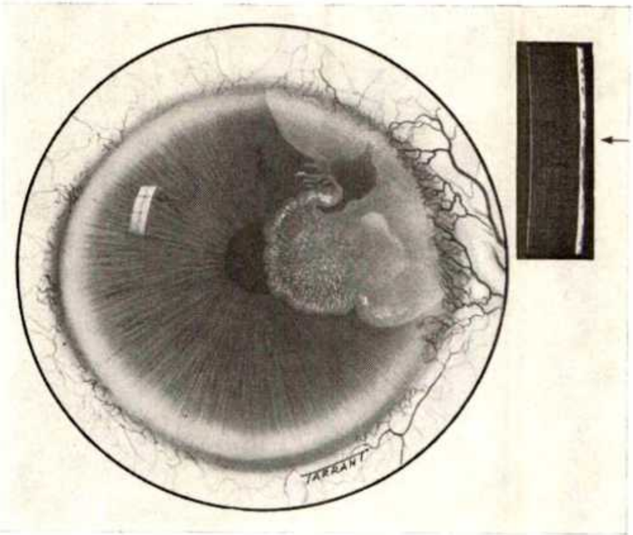

FIG. 1 *Clinical and slit-lamp appearances of the epithelial lesion*

PATHOLOGICAL FINDINGS

Light microscopy showed a disordered epithelium, in which the cells were pleomorphic and disorientated (Fig. 2), covering all but the edges of the specimen. The nucleo-cytoplasmic ratio was increased while the nucleoli were invariably enlarged and frequently multiple. Giant cells were not uncommon most of them containing multilobulated or even several nuclei. Mitotic activity was increased and was not confined, to the basal cell layer. The thickness of the epithelium, though in places marginally increased, was commonly within normal limits. At the periphery of the lesion the

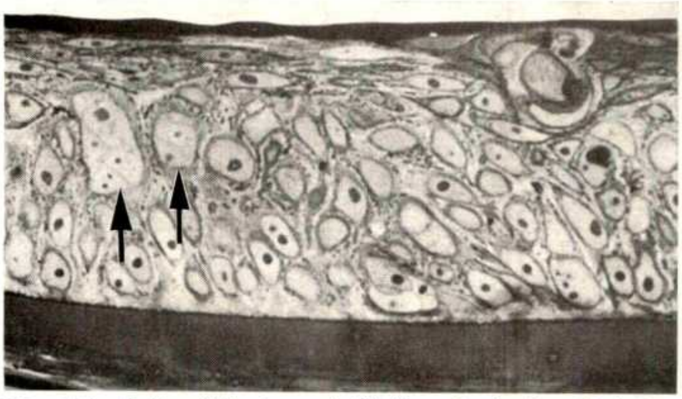

FIG. 2(*a*) *Section of the abnormal epithelium, showing loss of polarity, nuclear enlargement with occasional multilobulation and giant cell formation (arrowed), prominent multiple nucleoli, and (on the right of the picture) a dyskeratotic cell encircled by non-keratinized cells*

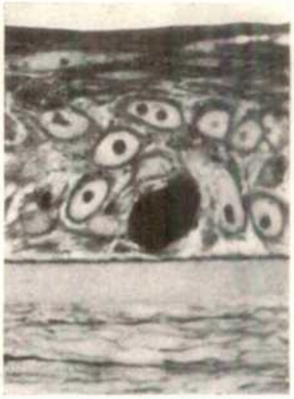

FIG. 2(*b*) *An epithelial cell, showing advanced dyskeratosis, is present in the basal cell zone*

Araldite sections, toluidine blue. ×440 junction between disordered and normal epithelium was clearly defined, with a tendency for the abnormal tissue to over-ride the surface of the healthy epithelium (Fig. 3).

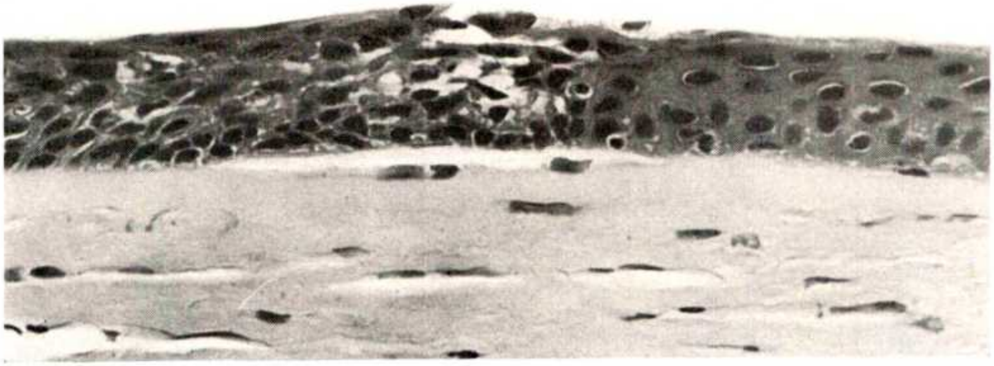

FIG. 3 *The junction between normal and malignant epithelium is abrupt. Haematoxylin and eosin.* ×320

Some red blood cells were present on the surface of the cornea and were occasionally trapped between the epithelium and an intact basement membrane. There was, however, no vascularization of the stroma, except for a restricted zone near the limbus, and it seems probable that the subepithelial incarceration of blood cells was an artefact incurred at operation. No abnormality was observed in Bowman's membrane or the superficial stroma.

Electron microscopy generally amplified the histological findings, the multilobulate morphology of occasional giant nuclei being particularly well demonstrated (Fig. 4, opposite). In addition, there were several features not apparent by light microscopy. Thus, a marked finding was a reduction in junctional complexes and interdigitations between individual epithelial cells, although such desmosomes as were present appeared to be normally formed. Also, while many cells showed a pronounced perinuclear arrangement of tonofilaments bound into bundles (Fig. 5), occasional cells showed more advanced signs of dyskeratosis (or individual cell keratinization) in the form of even more marked condensation of tonofilaments with either pyknosis or dispersion of the nucleus (Fig. 6); in late stages of this process the whole cell content was reduced to an homogeneous electron dense mass. Such cells were sometimes engulfed or "cannibalized" by neighbouring non-keratinized cells.

Comment

In that the histological and ultrastructural changes in this lesion are essentially the same as those that have been described in frank carcinoma of the corneal epithelium, there would seem reasonable to regard the appearances as being diagnostic of carcinoma *in-situ*. As such it is a pre-invasive carcinoma and rather more than a pre-cancerous disorder. Nevertheless, the lack of basement membrane disruption and the abrupt transition from abnormal to healthy epithelium is strongly in favour of conservative treatment in the form of local resection, such as was undertaken in this case. Even frank carcinoma is rarely associated with significant invasion of the corneo-scleral stroma and a similar conservative approach to therapy has been advocated on several occasions (Ash and Wilder, 1942; Irvine, 1963; Zimmerman, 1969). The propensity for intraepithelial carcinoma to recur after simple excision is possibly somewhat in excess of 10 per cent. according to Irvine's figures but regrettably from a prognostic standpoint, according to the same author, the likelihood of this occurring is not closely related to the degree of histological disturbance (Irvine, 1963).

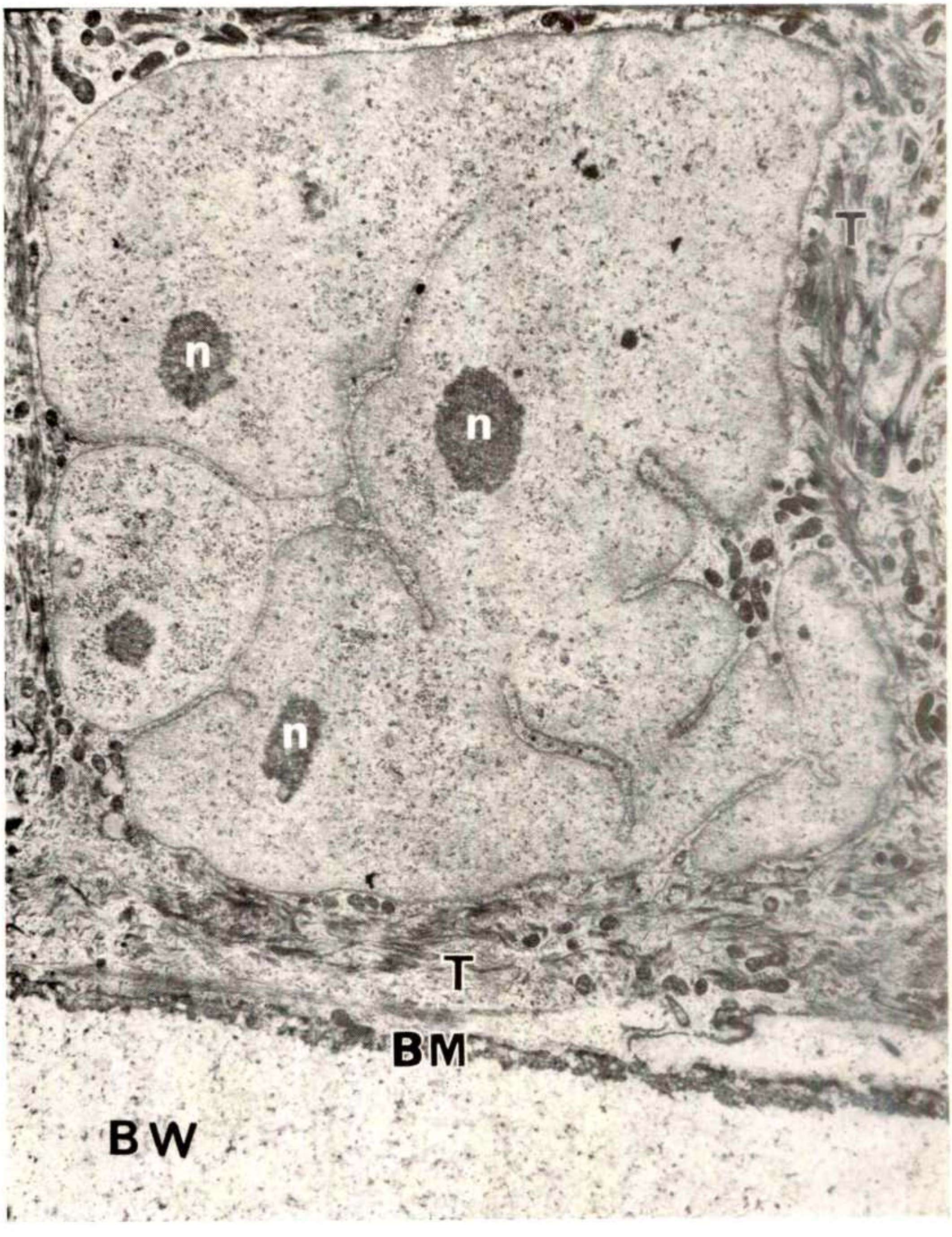

FIG. 4 *Electron micrograph of a giant epithelial cell containing a multilobular nucleus*

n = nucleoli, T = tonofilaments, BM = basement membrane, BW = Bowman's zone of the stroma. × 9,000

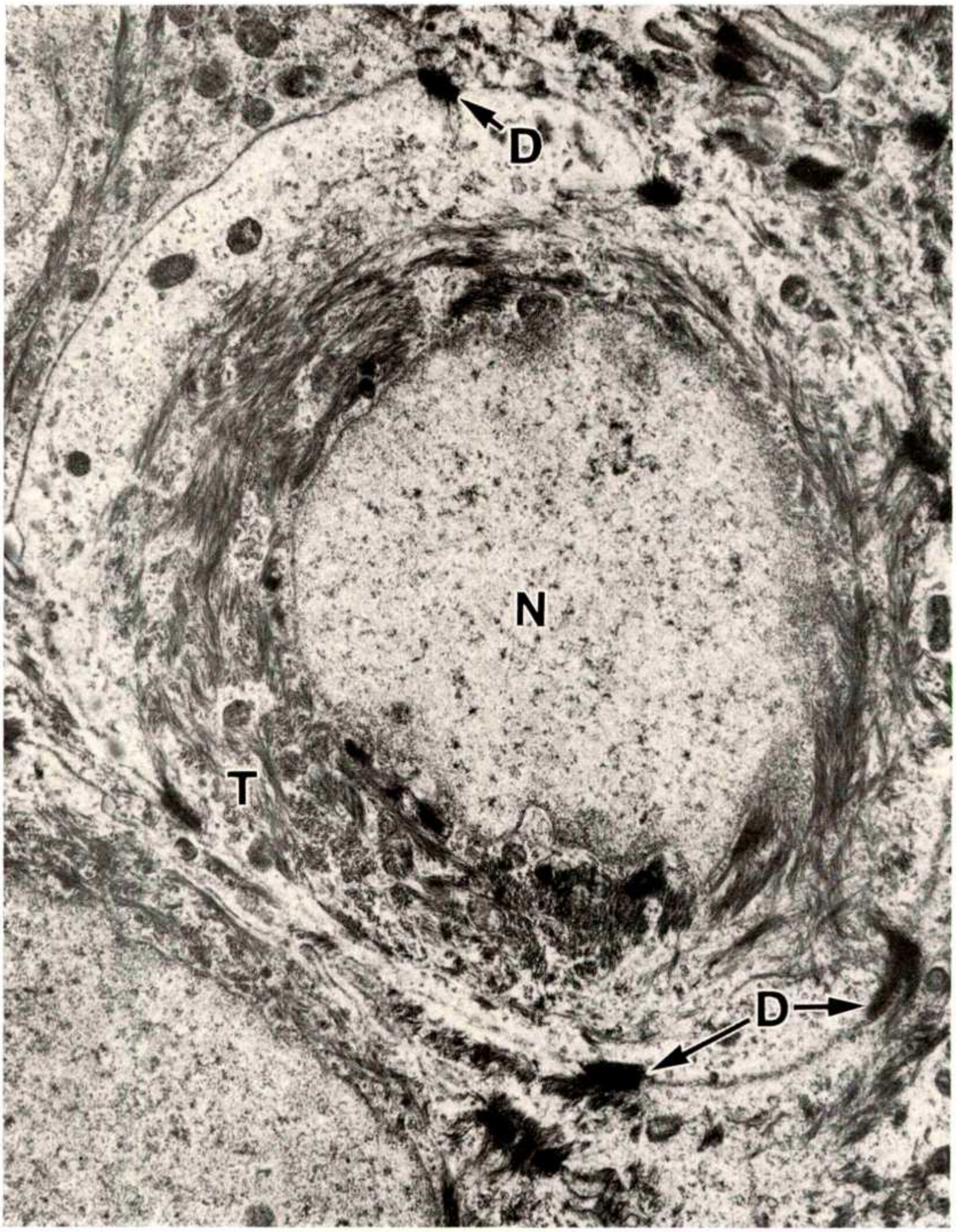

FIG. 5 *Electron micrograph of an epithelial cell, showing perinuclear arrangement of the tonofilaments* (*T*) N = nucleus, D = desmosomes. ×18,000

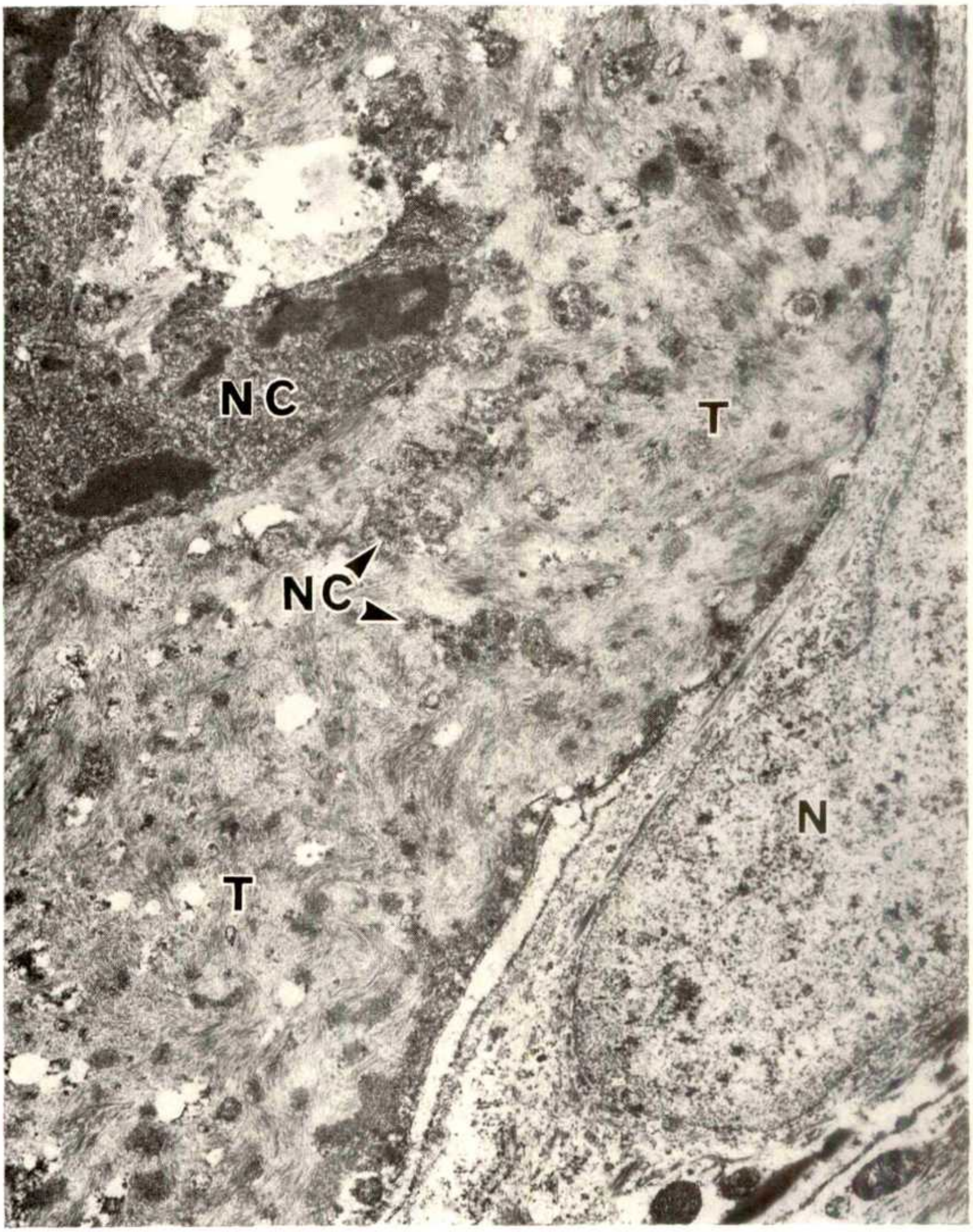

FIG. 6 *Electron micrograph of part of the dyskeratotic cell depicted in Fig.* 2(*b*), *showing a dense aggregation of tonofilaments admixed with degenerate and dispersed nuclear components* (*NC*)

N = Intact nucleus of an adjacent non-keratinized cell. ×24,000

In several respects the clinical appearances of the present case were unusual. Thus, in most reported instances, the underlying stroma is vascularized and moderately infiltrated with chronic inflammatory cells, whereas the present case showed only a few vessels limited to the periphery of the cornea and no inflammation. Again, in the present case, there was in general no significant elevation of the corneal surface in contrast to the usual description of a slightly raised lesion. Possibly these departures from the typical findings are indicative of an early lesion. It should be stressed, however, that while the diagnosis may be suspected on clinical grounds, proof is dependent on histological examination.

Summary

A case is presented of intraepithelial squamous cell carcinoma (Bowen's disease) of the cornea together with light and electron microscope findings.

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Fluorescein angiography of the anterior segment

Its value in corneal disease

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In conjunctival and corneal diseases, invasion of the corneal substance by vessels is often the forerunner of more serious disease. The study of vessels in detail is of importance in the assessment of such disease processes and, in particular, in following their natural history and response to treatment.

Reports of fluorescein angiography of the anterior segment have generally concerned the microvasculature of the iris. Vannas (1969) described in some detail his technique of fluorescein photography, and demonstrated the angiographic findings in pseudoexfoliation of the lens capsule and in various types of glaucoma. The effects of iris disease on the fluorescein pattern have been reported by other workers; Cobb (1968) noted the fluorescence of vascular tufts at the pupillary margin, which he later noted were particularly common in myotonic dystrophy (Cobb, Shilling, and Chisholm, 1970). The only report concerning the fluorescence of the microvessels found in corneal disease has come from Mitsui, Matsubara, and Kanawaga (1969), who demonstrated the vascular patterns associated with trachoma and with herpes simplex keratitis.

We have recently started serial photography of the fluorescence of abnormal vessels in diseased corneae, and the corneae of some 250 patients have been examined. In this report, selected records from some of these patients will be presented and discussed and their value assessed.

Materials and methods

The Zeiss photo slit-lamp camera was modified in the following ways in order to make it suitable for recording fluorescein angiograms. The power pack of the photo slit-lamp camera was replaced by a modified Zeiss Fundus Camera power pack. With this arrangement and the number 4 flash setting, firing at 2·0–2·5 second intervals could be achieved. The excitation filter used was of the absorption type (Zeiss 30 : 14 : 13) and was placed before the flash source. More recently a Balzar interference filter (FITC 4) has been used with greater success. A Kodak Wratten 15 barrier filter was placed in front of the camera objective. In order to view fluorescence as it appeared barrier filters were included in the eye pieces. Kodak Tri-X film was used (ASA 400) and this was developed for 12 minutes in ID 11 at 68°F.

Observations

TRACHOMA

Fig. 1 shows the angiogram of a patient with inactive trachoma. There is a localized patch of pannus demonstrated in the venous phase of the angiogram. The complex

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arcades of vessels are shown, and it can be seen that there is a mild leakage of fluorescein dye from the vessels of small calibre. The amount of leakage, though not great, is more than that which would be seen in normal limbal arcades. It is worth stressing that though the patient complained of minor irritative symptoms in this eye, the pannus in both eyes was clinically inactive; although superficial scarring was present, there were no infiltrates and there was no corneal oedema.

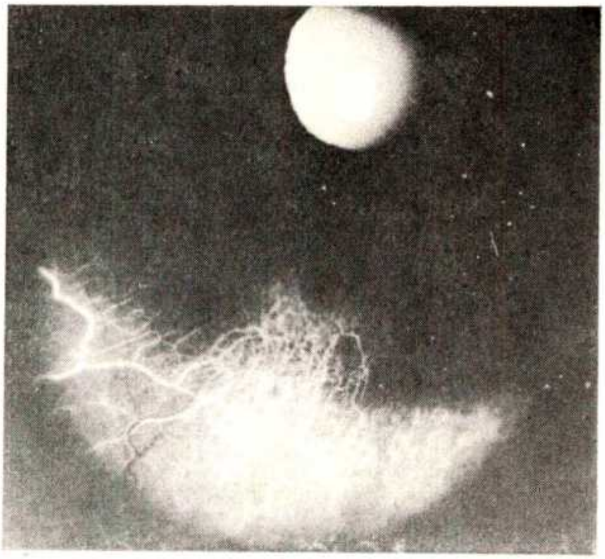


FIG. 1 *Microvascular anastomosis in the left eye of a patient with Grade IV trachoma*

A further point of some interest in this patient is that, despite a course of topical Predsol four times a day to the left eye for one week, no reduction occurred in the amount of leakage or in the form of the pannus. This contrasts, for instance, with the effect of steroids applied topically in a patient with a vessel-mediated homograft reaction, in which both reduction of leakage and regression of vessels occurred (Bron and Easty, 1969).

VESSELS IN CLEAR CORNEAL STROMA

The angiogram of vessels in the corneal stroma of an eye becoming phthisical after detachment surgery is demonstrated in Fig. 2. The vessels branch dichotomously and the branches of neighbouring systems interdigitate. Leakage occurs first from the terminal vessel loops, both afferent and efferent limbs, and is moderate in degree. It seemed likely that the case was one of anterior segment ischaemia, corneal vascularization having been recorded in this disorder (Sanders and Hoyt, 1969).

Why these vessels invade the optically clear corneal stroma is not known. Invasion in response to an ischaemic stimulus might be postulated. It might also be suggested that stromal oedema facilitates vessel entry. There is experimental evidence to show that aqueous humour production is reduced by interference with arterial supply to the ciliary body (Bárány, 1947), and ciliary body ischaemia with a reduction in the turnover of aqueous would be associated with a fall in aqueous oxygen tension. The resultant hypoxia of the posterior cornea could both produce oedema by interference with the endothelial pump and provide a stimulus for vessel ingrowth.

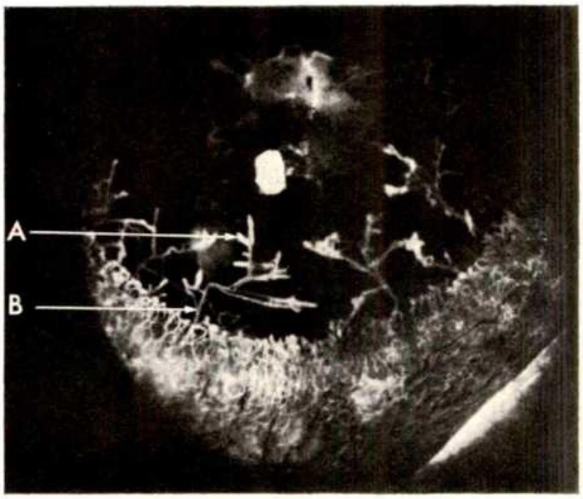


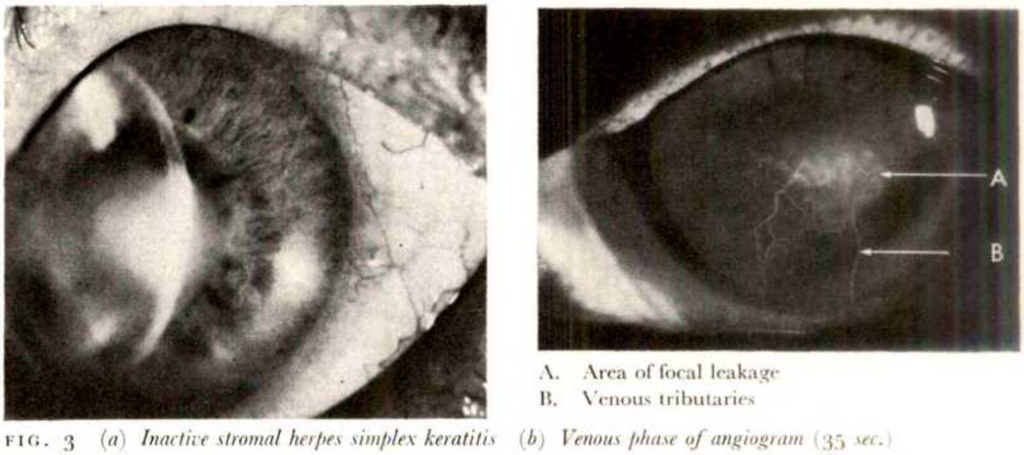
FIG. 2 *Fluorescein angiogram in a vascularized cornea after retinal detachment surgery* (36 *sec.*). *The eye was hypotensive*

A. Apical leakage

B. Fluorescing arterioles and venules in close apposition

ANGIOGRAPHY IN CLOUDY CORNEAE

Loss of corneal clarity may be due to corneal oedema, infiltration, or scarring, and to the deposition of material such as lipid. Whatever the cause of the opacity, fluorescein angiography often is able to demonstrate vessels which are difficult to photograph, or to observe clinically by slit-lamp examination. Fig. 3 demonstrates a central corneal lesion due to herpes simplex in a 56-year-old male patient with a long history of recurrent stromal disease in his left eye. The central cornea showed mild epithelial and stromal oedema but clinically there was no active keratitis. Angiography was performed shortly before corneal grafting. In Fig. 3*b* the vascular network is clearly shown in the venous phase of the dye transit (35 seconds). There is a definite difference in behaviour between the axial and the peripheral portions of the vessel network with respect to leakage. There is focal leakage of a mild degree from the terminal vessel loops, but none from the proximal arcades. There is thus a clearly-defined functional difference between the two areas. It may be noted that the survey photograph of the cornea completely failed to demonstrate the complexity of the vascular network (Fig. 3*a*).



A. Area of focal leakage
B. Venous tributaries

FIG. 3 (*a*) *Inactive stromal herpes simplex keratitis* (*b*) *Venous phase of angiogram* (35 *sec.*)

Fig. 4 (overleaf) shows the angiogram of stomal herpes affecting the upper cornea of the

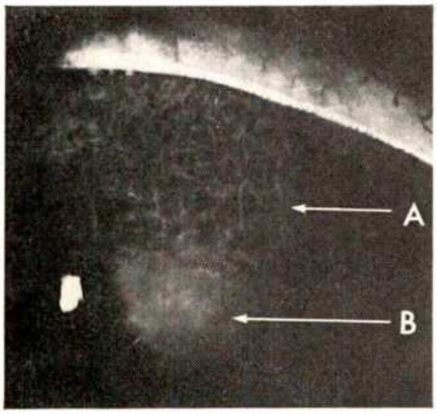


FIG. 4 *Vascular anastomosis in stromal herpes simplex keratitis* (*7 sec.*)

A. Proximal vascular plexus

B. Central zone of fluorescein leakage

left eye in a 60-year-old male patient. The affected cornea was grossly oedematous and vascularized, and the question whether active disease was present became important. In the fluorescein angiogram at 7 seconds the upper portion of the lesion can be seen to be well vascularized, with a complex arrangement of large venules and small arterioles. The illustration demonstrates moderate leakage towards the axial edge of the lesion. The degree of leakage is not as great as that encountered in the presence of the typical vasculitis seen in active herpetic keratitis. It is therefore likely that the stromal oedema is due more to endothelial dysfunction than to an active keratitis.

Lipid deposition may occur in the cornea in various conditions. It is a comparatively common occurrence and in the majority of cases it is difficult to understand the mechanism. Duke-Elder (1968) has summarized the literature and classified corneal lipid deposition into three fundamental groups. It may be primary, in which case it is deposited in an apparently normal cornea, or secondary, in which case it represents a terminal change occurring in degenerating cells. Under the term "lipid keratopathy" are grouped those cases in which the appearance of fat is preceded by corneal vascularization. It is noteworthy that the intensity of intravascular fluorescence and of fluorescein leakage may vary considerably from case to case.

Lipid deposition is a common occurrence after ophthalmic herpes zoster (Cogan, 1960). In a 57-year-old female with a crystalline deposition in a peripheral corneal scar

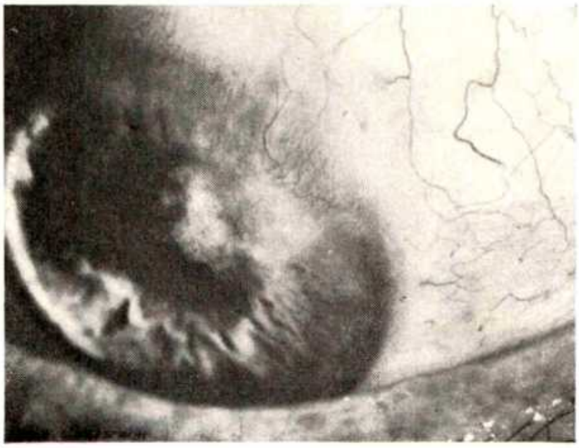


FIG. 5 (*a*) *Paralimbal lipid keratopathy*

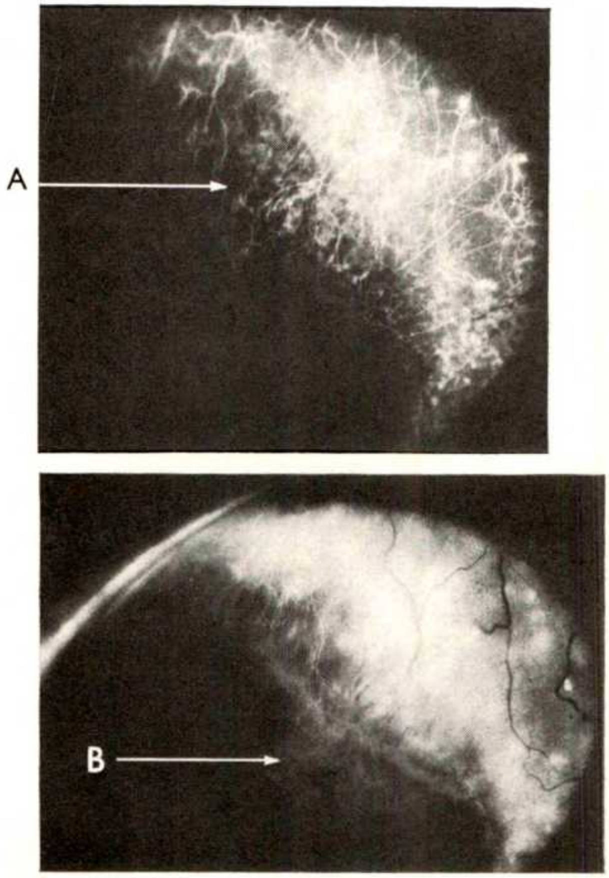


FIG. 5 *(b) and (c) Angiography at 30 and 70 seconds respectively*

A. Proximal zone of vascularization, showing early leakage

B. Distal zone of vascularization appearing as an area of faint leakage

in the left eye (Fig. 5*a*), the fluorescein angiograms demonstrated only moderate intravascular fluorescence at 30 seconds (Fig. 5*b*), and leakage into the stroma at 70 seconds was comparatively slight (Fig. 5*c*).

Fig. 6 shows a peripheral, post-zoster corneal scar with lipid deposition in the left eye of a 57-year-old female patient. The deposition was made up of a deep and a superficial

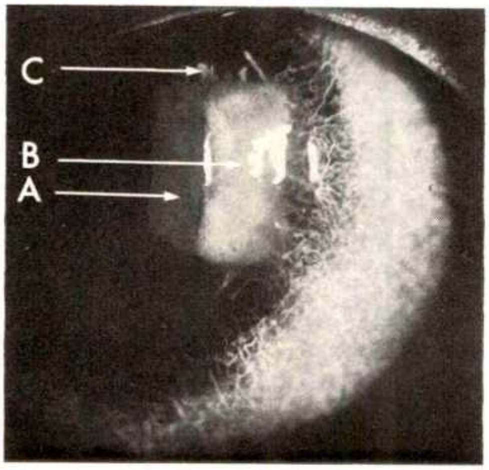


FIG. 6 *Angiogram in a case of lipid keratopathy after an attack of herpes zoster ophthalmicus* (22 sec.)

A. Deep lipid deposits

B. Superficial lipid deposits

C. Stromal vessels hidden by the pseudofluorescence of the superficial plaque lamella, one lying anterior to the other. In this case the density of the anterior deposit has been sufficient to obscure the disposition of the deep set of vessels seen on angiography.

Fig. 7*a* shows the cornea in a 50-year-old man whose eyes were injured in a chemical explosion 16 years before, when a mixture of poorly nitrated dichlorobenzene and sulphuric acid splashed into both eyes. Diffuse scarring of the left cornea with marked lipid

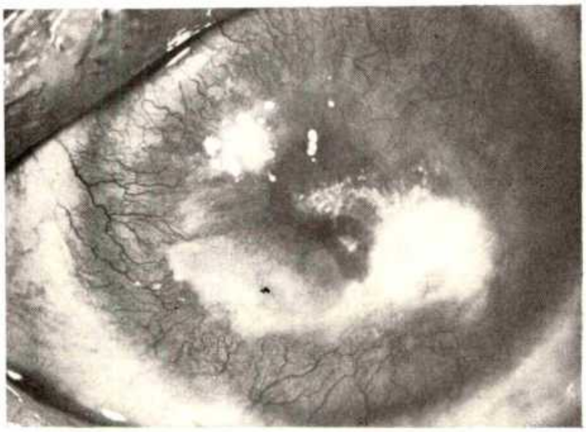


FIG. 7 (*a*) *Corneal appearance in a patient with lipid keratopathy following a chemical injury*

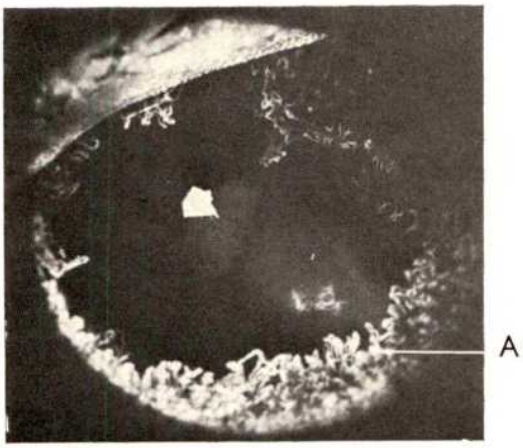
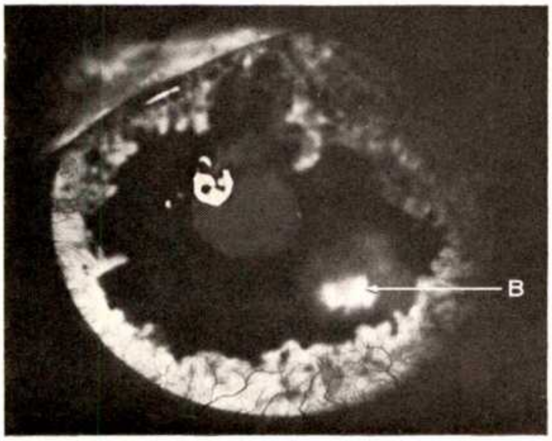


FIG. 7 (*b*) *and* (*c*) *Early and late angiograms at 20 and 47 sec. respectively*

A. Extensive superficial pannus



B. Intense leakage in stroma in relation to a lipid deposit deposition occurred, but it was of interest in that this did not develop until some years after the original injury. The history is reminiscent of the natural history of mustard gas keratitis, and the similarity was borne out by the presence of aneurysmal dilatations of the veins of the conjunctiva. The angiograms are shown in Fig. 7*b* and *c*. The main feature of the early angiogram is an elaborate circumferential pannus. In the later angiogram an island of localized leakage of high intensity is seen in the lower temporal quadrant of the cornea. This corresponds to a plaque of dense lipid deposition. The apparent isolation of this vascular zone from the periphery is due to masking of the vascular supply by the corneal scar.

An interesting situation occurred in a 44-year-old female with extensive peripheral lipid deposition in both corneae of over 20 years' standing. On biomicroscopy, a number of radial vessels were visible, but the degree and complexity of the deeper vessels could not be appreciated. Fig. 8 shows the fluorescein angiogram taken 22 seconds after the initial injection. A fine and intricate plexus is clearly demonstrated. The capillaries form arcades between the arterioles and venules leading to a regular and complex architectural arrangement. The angiogram is of interest because the intensity and speed of onset of the leakage were remarkable and the eye showed no signs of clinical activity. Furthermore, the angiogram suggests that the predominant source of supply to the capillary plexus is provided by the superficial perilimbal arterioles. It seems likely that the lipid has been deposited in a superficial pannus. Certainly the distinctive pattern with its regular architecture is entirely different from that seen in other cases of lipid deposition in the cornea so far described.

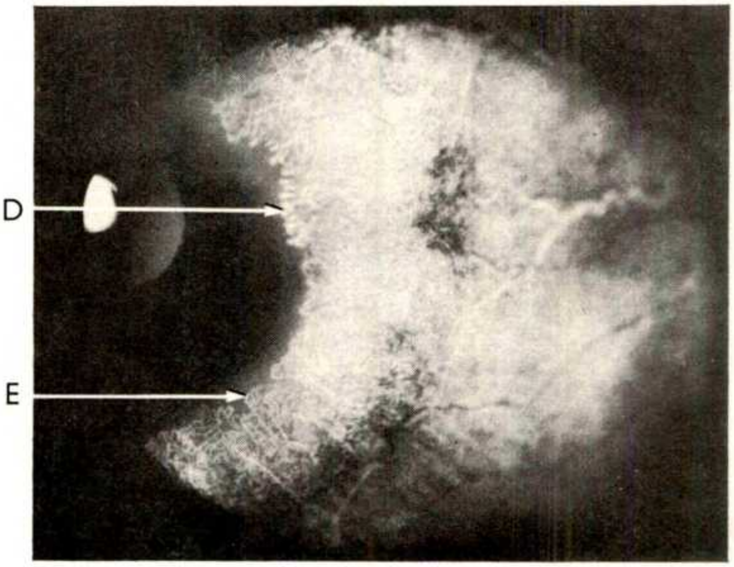


FIG. 8 *Fluorescein angiogram in the right eye of a 44-year-old woman with a dense lipid keratopathy* (22 *sec.*)

D. Early leakage in some areas

E. Fine capillary network

VESSELS AND CORNEAL GRAFTING

A study of vessels in the corneal graft situation is of importance; their presence is undesirable in the donor disc, chiefly because of their significance in the production of a homograft reaction. Fig. 9 (overleaf) shows a penetrating graft for a herpetic stromal abscess 16 days after surgery. The graft was performed through a previous lamellar graft. It was optically clear at the time of examination and continued to remain so. The angiogram shows the disposition of vessels at the interface of the earlier graft. The irregular vascular ring is fed by radial vessels. Deeper vessels in the bed of the lamellar graft pass to the new graft interface, and there is a diffuse and moderate leakage, which however does not transgress the graft–host junction.

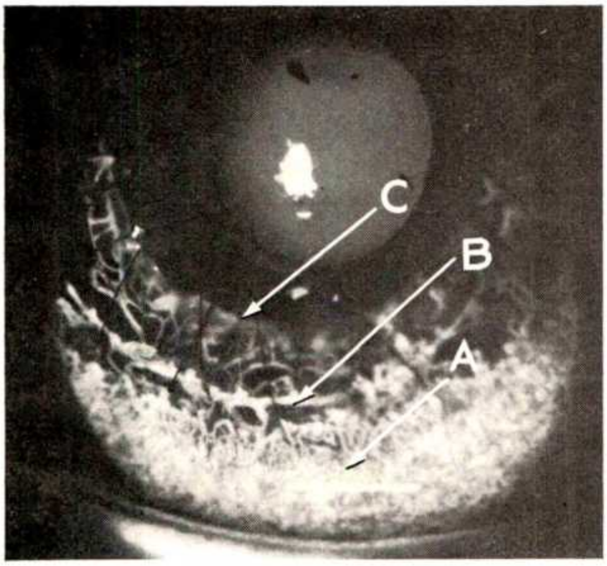


FIG. 9 *Vascularization at the interface in a 7-mm. penetrating graft after an herpetic stromal abscess* (27 *sec.*)

A. Limbus

B. Lamellar graft-host junction

C. Penetrating graft-host junction

Fig. 10 shows the cornea in a 27-year-old male grafted 5½ months previously for central scarring due to stromal herpes simplex. The angiogram shows the vessels passing to the graft-host junction. The eye was quiet on a regime of Predsol drops four times daily. It is seen that the vessels fluoresce faintly and although leakage occurs it is minimal. Vessels do not enter the graft itself.

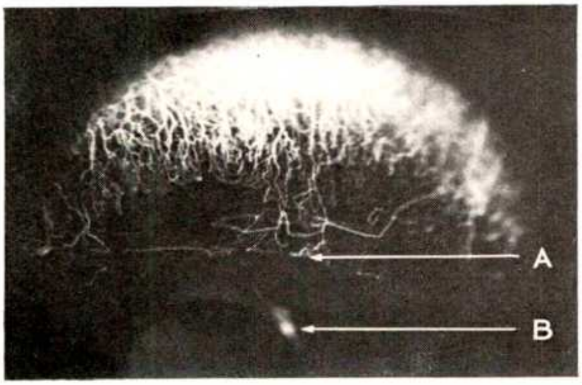


FIG. 10 *Angiogram of vessels reaching interface of a penetrating graft* (24 *sec.*)

A. Position of interface

B. Point of focal leakage from iris at pupil margin

In a 57-year-old female patient, who had been grafted on four occasions between 15 and 19 years ago for left herpetic keratitis, the final graft became cloudy after endothelial decompensation (Fig. 11*a*). The dense plexus of vessels in the recipient cornea is shown in Fig. 11*b*. Small vessel twigs may be seen passing into the temporal edge of the graft between the twelve and 4 o'clock meridians. Leakage into the host cornea is pronounced. Leakage into the graft cornea, however, seems to be related to the presence of vessels in the graft itself (Fig. 11*c*); it is therefore seen within the temporal edge of the graft in relation to the vascular twigs, but it is virtually absent on the nasal side. Here, the host vessels do not reach the graft-host junction. The sharp contrast between the fluorescence of the host and donor corneae delineates the interface. This implies there is a definite barrier to diffusion across the interface.

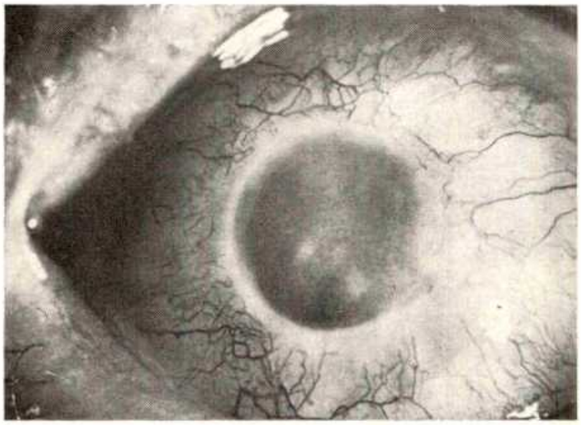
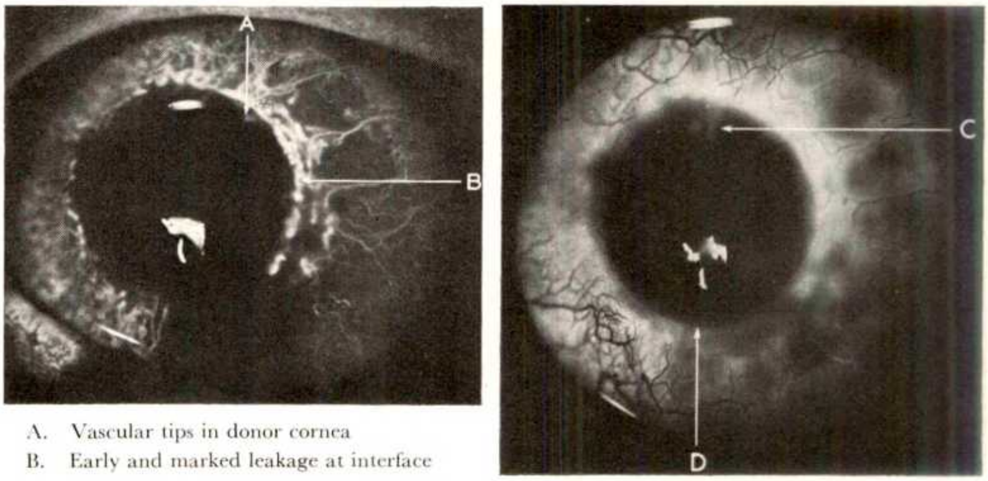


FIG. 11 (*a*) *Unsuccessful penetrating graft*



A. Vascular tips in donor cornea
B. Early and marked leakage at interface

C. Leaking vessels in donor cornea
D. Interface sharply demarcated

FIG. 11 (*b*) *and* (*c*) *Angiograms at* 26 *sec. and* 1 *min.* 38 *sec. respectively*

Discussion

In assessing the value of fluorescein angiography of the anterior segment, one must first determine what information it is able to provide. Fluorescein angiography of the retina reveals a stereotyped vascular system in which there are clear arterial, capillary, and venous phases of the dye transit. Against such a background, abnormalities in vascular pattern can be clearly demonstrated.

In fluorescein angiography of the cornea, the information that can be gathered is entirely different in nature. The cornea is an avascular tissue, and so the very existence of vessels represents an abnormality. There is therefore no stereotyped pattern of normality in vascular anatomy with which to compare the abnormal. However, fine vascular plexuses which are difficult to record with accuracy by drawings or photography are clearly demonstrated by intravascular fluorescein and photography, though it is often more difficult to observe arterial and venous phases. This may be because the rate of circulation appears to be rapid and the arterial phase may be easily missed. At the same time, a diseased cornea may be invaded by many plexuses in which each vascular bed is distinct. Hence it is unlikely that arterial and venous phases will be in phase with each other, which adds to the problem of interpretation.

Leakage of dye from the vessels is a prominent feature of angiography of the globe and the vascularized cornea is no exception. The concept of damaged vessels leaking material into the tissues is an old one and the temptation to equate leakage of fluorescein dye with an increase of vessel permeability is difficult to resist. In the study of the microvasculature of the retina by the technique of fluorescein angiography, this interpretation is entirely justified, for healthy retinal capillaries are impermeable to fluorescein and leakage of the dye in the retina does indicate pathological permeability of these vessels. However, the behaviour of the retinal capillaries, and to some extent of the cerebral capillaries, differs from that of capillaries in tissues in other parts of the body (Hill, 1969). The capillaries of the skin, conjunctiva, kidneys, and peritoneum, for instance, readily allow free fluorescein to escape from the plasma. It has been demonstrated experimentally that the retinal vessels possess an active transport mechanism which prevents the movement of the fluorescein anion out of the vessel lumen (Cunha-Vaz and Maurice, 1966). This accounts, in part, for the impermeability of healthy retinal vessels to fluorescein during angiography; the behaviour of the conjunctival vessels and of vessels in the vascularized cornea suggests that they do not possess such a mechanism.

Up to 85 per cent. of fluorescein in the blood is bound to plasma protein, chiefly to albumin, while the rest is free and occurs chiefly in the anionic form at blood pH (Hodge and Dollery, 1964).

In pathological terms increased vessel permeability is characterized by the passage of colloids and cells from the blood stream into the tissues. Of the colloid particles, the smallest molecules will pass out more readily than the largest, so that albumin will pass out more readily than globulin. It is clear that the leakage of fluorescein from healthy conjunctival vessels must involve the loss of free fluorescein anions into the extracellular space. In the presence of inflammation, an increasing loss of albumin-bound fluorescein from the vessels would occur, in addition to the loss of free fluorescein.

Theoretically, there are two ways by which fluorescein may be lost from the capillary lumen: by diffusion along a concentration gradient, and by bulk flow of fluid, that is, as a result of a net loss of fluid from the intravascular to the extravascular compartment. The rate of diffusion will depend on the concentration of dye in plasma and on the resistance of the endothelial barrier to the diffusion process. Increase of endothelial permeability associated with inflammation not only allows protein-bound dye to diffuse from the vessel, but also reduces the resistance to diffusion of the free dye, so that both components are increased in the tissue fluids.

The contribution of bulk flow of fluid to the transfer of fluorescein across the vessel endothelium depends largely on the magnitude of the bulk flow in the body tissues. This in turn depends on the balance of hydrostatic and colloid osmotic forces acting inside and outside the vessel lumen. These factors determine the effective filtration pressure driving fluid across the capillary endothelium. The cornea differs from other tissues in that it possesses a highly negative fluid pressure in the stroma in the deturgesced state. The stromal fluid pressure has been estimated to be in the region of -40 mm.Hg in the living eye (Mishima, 1968), whereas the interstitial pressure in subcutaneous tissue is said to vary from zero to -7 mm.Hg (Guyton, 1966). For this reason the effective filtration pressure would be high across vessels in the cornea of normal thickness compared to vessels in other tissues, and bulk flow from these vessels may be expected to be higher as a result. However, it must be remembered that the stromal lamellae are tightly packed and form a definite barrier against the bulk flow of fluid. It must therefore be supposed that fluorescein escapes from vessels into the stroma by means of diffusion, and that transport by bulk flow is of minor importance. The cornea, therefore, does not differ from other tissues, in which the vessels lose small molecules by means of diffusion rather than by bulk flow (Pappenheimer, 1953).

In the inflamed cornea, the leakage of dye is often increased, and it is possible that this depends upon the increased flow rate, permeability, and total area of permeable endothelium. It has been shown that, in active inflammatory corneal disease, the leakage of fluorescein is intense, and that as the inflammation dies down the leakage is reduced. But there are certain situations in which the leakage is intense in the absence of apparent inflammatory disease. Patients with lipid keratopathy may demonstrate intense leakage without serious inflammation and it is possible that this may be related to the process of lipid deposition.

The corneal graft situation is one in which fluorescein angiography might be expected to be of value. In a straightforward corneal graft, host vessels start to pass towards the donor button but, instead of penetrating the graft, they either cease their centripetal growth before reaching the graft, or having reached it take a circumferential course along the graft-host interface. Fluorescein angiography shows whether fine vessel twigs enter the graft and provides a permanent record against which the further movement of the vessels may be assessed. The entry of host vessels into the graft is of importance, not only because of the immediate danger of a vessel-mediated homograft reaction but because at a later stage, when the eye is quiet and the graft clear, such vessels may still carry blood and may dilate in response to non-specific inflammatory stimuli. The graft is then exposed to the danger of a homograft reaction as a late event.

The interpretation of leakage from vessels in the neighbourhood of a graft requires careful consideration. There does seem to be some sort of barrier to the diffusion of dye within the stroma from host to graft. However, the barrier is not absolute and some dye does pass across the interface. This is particularly true when a circumferential vessel passes along the interface for some distance, an occurrence which is not uncommon. It would be easy to interpret the movement of fluorescein across the boundary as significant in the immune processes leading up to a homograft reaction. But it must be remembered that the dye is only a marker, either in the form of free anion, or bound to albumin. Whatever the form, when we are considering the efferent limb of the non-cellular component of the graft reaction, we are concerned with globulin, not albumin, and it is known that the resistance to diffusion of molecules through corneal stroma is greatly affected by molecular size (Maurice, 1969).

One form of leakage has been mentioned only in passing, but is seen quite frequently. Although leakage is usually most developed at the apical tips of arterio-venous loops or within more complex capillary plexuses, it is often seen along the larger vessel trunks, particularly the veins, in a late phase (Fig. 4). This perivenous leakage is probably a true loss of dye through the vessel walls (Zweifach, 1966), but other alternatives may be considered. Lymphatics are absent from normal cornea except at the limbus, but they are known to be present in vascularized corneae (Collin, 1966) and it is therefore possible that protein-bound fluorescein may be removed from the cornea in part by this route and may become visible. It is also possible that dye may diffuse in the stroma from a site of intense vessel leakage, centrifugally along main vessel trunks passing to and from the lesion. It should not be difficult to investigate in histological material whether a perivascular space exists around such vessels.

Summary and conclusions

A technique of fluorescein angiography has been developed for the study of microvessels in the diseased cornea. Simple modification of the Zeiss photo slit-lamp camera allows photographs of good quality to be made at a frequency of one exposure every 2·0 to 2·5 seconds. Selected examples from some 200 patients are presented and discussed. It is concluded that the method is of value in accurately recording complete vascular patterns in the cornea, and in particular that it may be used in assessing changes in vascularity over a period of time. It has been used effectively in following the response of corneal disease to therapy. The significance of the leakage of fluorescein from microvessels is discussed, and it is pointed out that, while no simple conclusion can be drawn about this process when comparing cases, it may be of some value in following a condition in an individual case over a period of time. In the latter situation, it may reflect changes in the inflammatory activity of a disease process.

We gratefully acknowledge the interest and encouragement of Professor Barrie Jones in this work and the help of the Audio-Visual Department at the Institute of Ophthalmology in the preparation of the illustrations. Thanks are also due to Dr. D. F. Cole and Dr. L. J. Youlten for many helpful discussions. Fig. 11 is reproduced by kind permission of the Editorial Committee of the *Transactions of the Ophthalmological Society of the United Kingdom*.

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Ocular manifestations in angiokeratoma corporis diffusum (Fabry)

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Angiokeratoma corporis diffusum (Fabry), originally described as a rare skin anomaly, is now recognized as an inborn error of metabolism. This anomaly is due to a mutation in the X-chromosome, with serious consequences for the male patient. In female carriers the expressivity of the abnormal gene varies greatly, but is rarely as serious as in males.

Symptoms and course

The diagnosis in males can usually be made on the skin lesions, the numerous dark red macules and papules, appearing in the second decade. Severe pain in the hands and feet, increasing in heat and cold, is the first serious complaint. At a later stage the vascular anomalies in the heart and kidneys become a prominent feature. Renal failure is the usual cause of death, which occurs in the fifth decade of life. In other cases neurological symptoms prevail. In a few cases in males symptoms may be absent. In females symptoms are usually less severe and may even be absent. All cases, regardless of the presence of skin lesions, can be diagnosed by skin biopsy. An abnormal lipid can be demonstrated by special staining techniques in the endothelium and muscular wall of the vessels of all calibre (Ruiter, 1953) (Fig. 1). The storage of the substance in various organs leads to the different signs and symptoms of the disease. The nature of the lipid had long been obscure, but has now been shown by Sweeley and Klionsky (1963) to be a glycolipid. The metabolic disorder was identified as a deficiency in ceramide trihexosidase (Brady, Gal, Bradley, Martensson, Warshaw, and Laster, 1967).

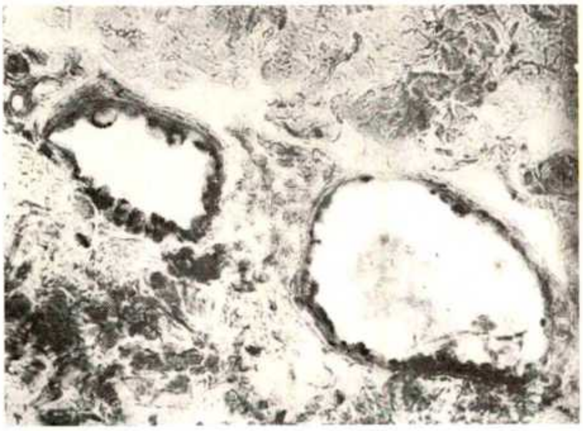

FIG. 1 *Lipid in vascular walls stained with Sudan black*

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Ocular symptoms

In patients with angiokeratoma and serious renal involvement, hypertensive retinopathy can occur, as Wallace (1958) described in one of his cases. These findings are not typical of the disease. The ocular symptoms which typically occur in angiokeratoma were first described by Weicksel (1925).

(1) *Vascular lesions in conjunctiva and retina*

Conjunctiva The vessels of the bulbar and palpebral conjunctiva show ampullary and saccular aneurysms of the small venules with stasis and thrombosis in some cases.

Retina The vascular lesions in the retina consist of segmental dilatation and tortuosity of the venules. Tortuosity was also described in the arteries. The vascular lesions in conjunctiva and retina may be regarded as identical to the dilated vessels in the skin.

(2) *Corneal opacities*

These were described by Weicksel (1925), Pompen, Ruiter, and Wyers (1947), and Spaeth and Frost (1965).

The typical lesion is a whirl-like opacity in the superficial layers of the cornea (Fig. 2).

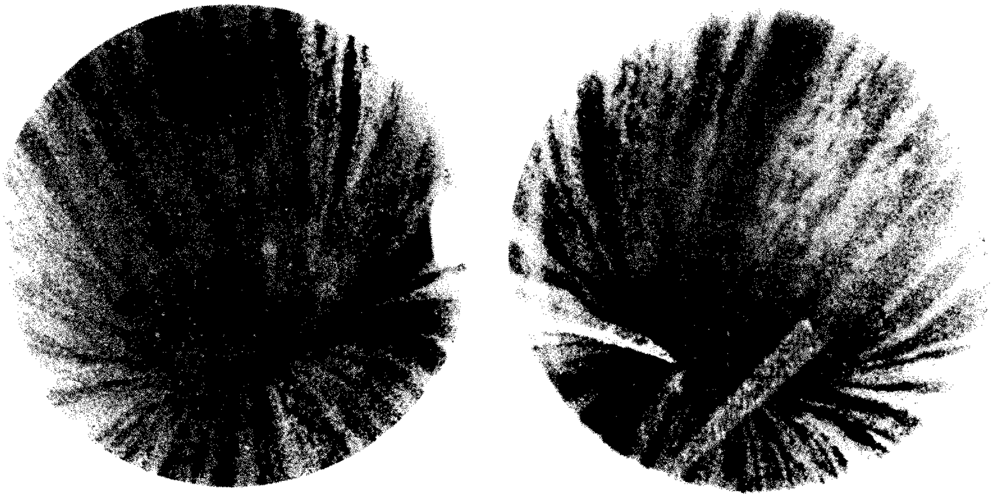

FIG. 2 *Slit-lamp photographs of corneal opacities in Case 12*

Streaks of a more or less dense opacity extend from near the centre of the cornea to the periphery. The lesion can be easily detected in some cases. In the majority of our patients, however, the corneal changes were slight, the earliest lesion being a diffuse corneal haziness (Patient 5).

The opacity is sometimes described as having a yellowish appearance, but was of a whitish dust-like character in our patients.

A histological study of the condition was carried out by Weingeist and Blodi (1971). They found intraepithelial storage, reduplication of the basement membrane, and amorphous material between basement and Bowman's membranes.

(3) *Opacities in the lens*

These were described in a number of cases by Spaeth and Frost (1965).

(4) *Anomalies of the disc*

Wallace (1958) described an irregular and slightly hazy border to the disc in two cases, both in the same family. In one of these, optic atrophy was also present. Spaeth and Frost (1965) mentioned peripapillary as well as perimacular oedema in one case. The condition seems to be rare, and was only found in one of our patients (Case 21). A slightly choked disc on both sides was seen during the development of severe neurological symptoms, which could be interpreted as disseminated sclerosis, but also could be caused by lipidosis. In this patient there was no hypertensive retinopathy. From this case as well as from the literature, it cannot be stated whether the choked or atropic disc is a typical finding in angiokeratoma.

Description of cases

Eighteen patients will be described. Cases 1 to 13 belonged to Family B (Fig. 3) and Cases 14 to 17 to Family F (Fig. 4).

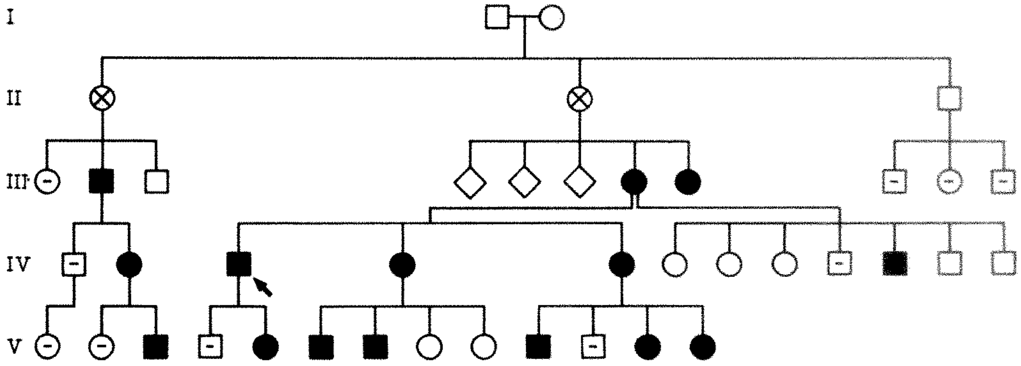

FIG. 3 *Family B*

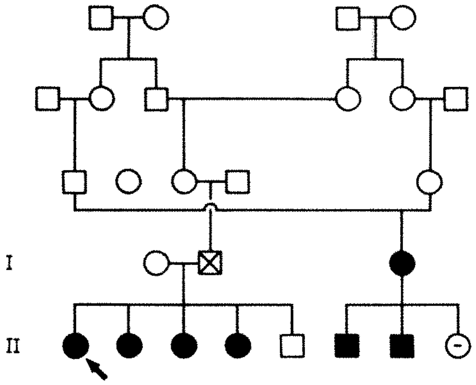

FIG. 4 *Family F*

■ ● examined positive
⊟ ⊖ examined negative
☒ ⊗ not examined: diagnosis probable
□ ○ not examined

Case 1, *a man aged* 37, proband; B, IV, 3.

OPHTHALMOLOGICAL FINDINGS

Conjunctiva In the right eye, in the temporal bulbar conjunctiva, a very irregular tortuous vessel was present (Fig. 5, overleaf).

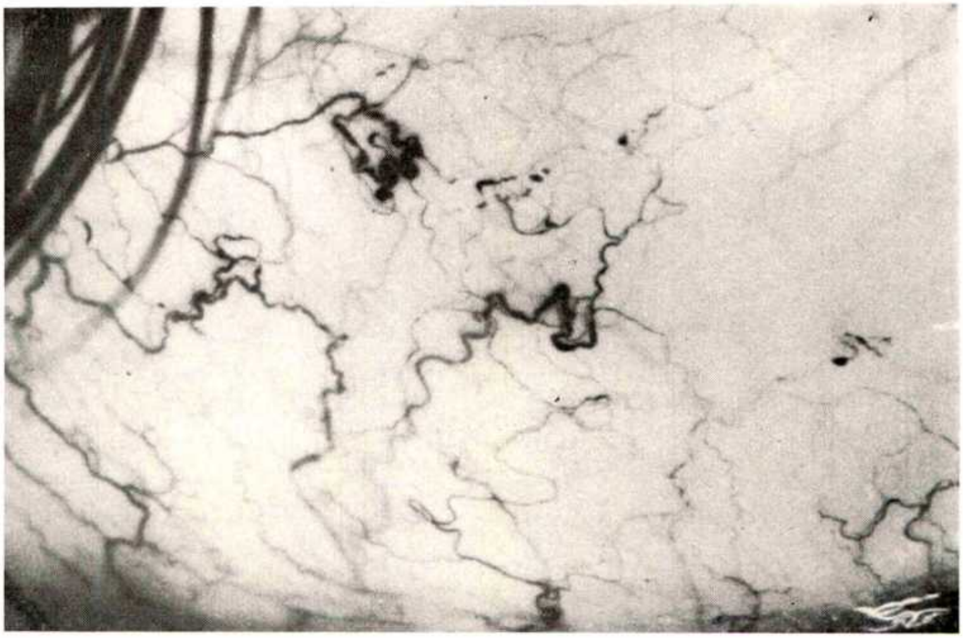

FIG. 5 *Tortuous conjunctival vessel in Case* 1

Corneae Both showed a few streaks of the typical superficial opacity.

Fundi In the right eye a segmental dilatation of the superior temporal vein was present (Fig. 6).

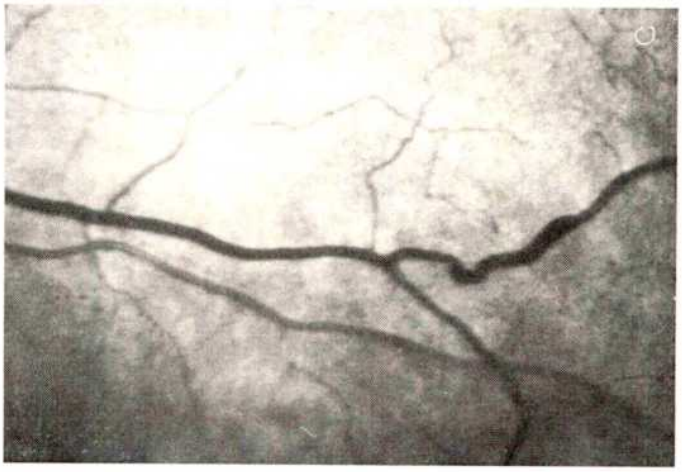

FIG. 6 *Segmental dilatation of retinal vein in Case* 1

SKIN

Typical lesions. Severe pain in hands and feet. No renal symptoms.
Biopsy positive for lipid staining.

Case 2, *a female aged* 34, sister of Case 1; B, IV, 4.

OPHTHALMOLOGICAL FINDINGS

Conjunctiva In the right eye, in the temporal bulbar conjunctiva, an irregularly dilated vessel was present, while some smaller vessels showed saccular distensions.

Corneae In both corneae, in the infero-nasal quadrants, some streak opacities were seen.

Fundi The retinal vessels showed no abnormalities.

SKIN

There were a few skin lesions. The biopsy was positive.

Case 3, *a girl aged* 8, daughter of Case 1; B, V, 5.

OPHTHALMOLOGICAL FINDINGS

Conjunctival vessels No abnormality was seen.

Corneae There was a very distinct vortex of streak opacities in the superficial layers of both corneae.

Fundi The retinal vessels were normal.

SKIN

There were no clinical symptoms. The biopsy positive for lipid staining.

Case 4, *a female aged* 56, mother of Cases 1 and 2; B, III, 7.

OPHTHALMOLOGICAL FINDINGS

In the skin of the left upper eyelid some dilated vessels were seen.

Conjunctiva The vessels showed no abnormalities.

Corneae A vortex of opacities was seen especially in the right eye.

Fundi In the left fundus the infero-temporal vein showed segmental dilatation (Fig. 7).

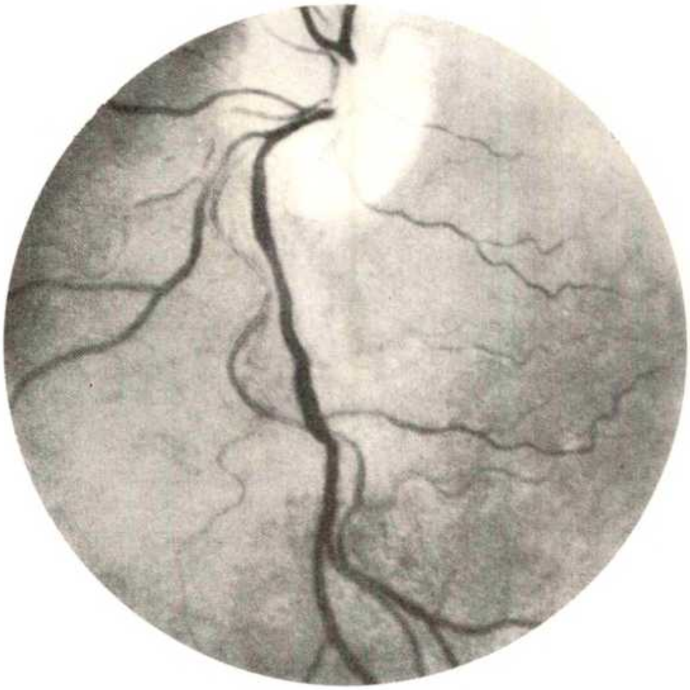

FIG. 7 *Segmental dilatation of the inferior retinal vein in Case 4*

SKIN

There were very few lesions. The biopsy was positive for lipid staining.

Case 5, *a boy aged* 11, son of Case 4, half-brother of Case 1; B, IV, 10.

OPHTHALMOLOGICAL FINDINGS

The conjunctival vessels of the left eye showed saccular aneurysms.

Corneae There was no vortex to be seen. A slight haziness of the superficial layer of the corneae was seen as if the epithelium was powdered. The condition is, however, difficult to differentiate from a normal appearance.

Fundi The left fundus showed tortuosity of the vessels at the posterior pole (Fig. 8).

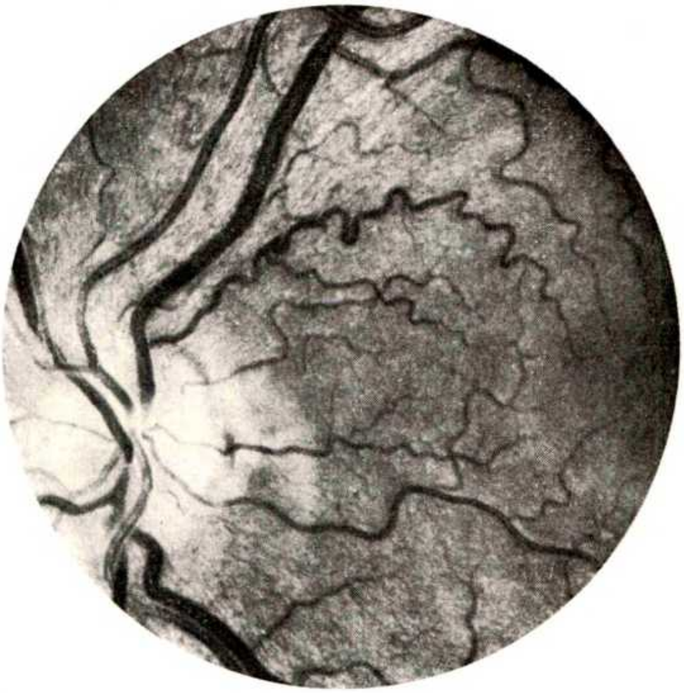

FIG. 8 *Tortuosity of retinal vessels in Case 5*

SKIN

There were no skin lesions. The biopsy was positive for lipid staining.

Case 6, *a boy aged* 9, son of Case 2; B, V, 6.

OPHTHALMOLOGICAL FINDINGS

Corneae In both nasal corneae the vortex of opacities was clearly seen.

Fundi There was no abnormality of the vessels.

SKIN

There were no lesions. The biopsy was positive for lipid staining.

Case 7, *a boy aged* 6, son of case 2; B, V, 7.

OPHTHALMOLOGICAL FINDINGS

Conjunctiva A distinctly dilated saccular vessel was to be seen temporally in the conjunctiva of the right and left eyes.

Cornea In the right cornea there was a horizontal streak. Only if the typical picture is known, can such a small streak be recognized.

Fundi No distensions were seen in the retinal vessels, but there was a very distinct tortuosity both of the arteries and venules.

As the patient was a small boy, no fundus picture could be taken.

SKIN

There were no lesions. The biopsy was positive for lipid staining.

Case 8, *a female aged* 34, sister of Case 1; B, IV, 5.

OPHTHALMOLOGICAL FINDINGS

Corneae A distinct vortex was to be seen in both corneae.

Fundi There was an irregularity of the lumen of the right superior temporal vein.

SKIN

There were a few lesions. The biopsy was positive.

Case 9, *a boy aged* 15; B, V, 10.

OPHTHALMOLOGICAL FINDINGS

Conjunctiva In the right and left eye on the temporal side, conjunctival vessels showed saccular distensions.

Corneae In the right eye the superficial vortex form opacity was clearly to be seen; in the left eye it was only of a very shadowy nature.

Fundi There was distension of the right inferior veins (Fig. 9).

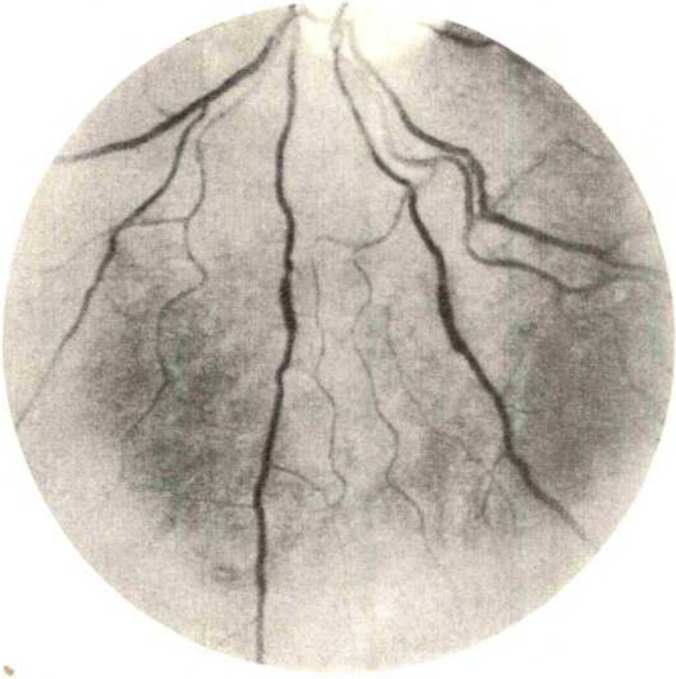

FIG. 9 *Segmental dilatation of right inferior vein in Case* 9

SKIN

There were lesions on the scrotum. The biopsy was positive for lipid staining.

Case 10, *a girl aged* 12; B, V, 12.

OPHTHALMOLOGICAL FINDINGS

Corneae In the left cornea on the nasal side, some radially arranged streaks were to be seen, as in Case 14. The right cornea showed no abnormality.

SKIN

There were no lesions. The biopsy was positive for lipid staining.

Case 11, *a girl aged* 6; B, V, 13.

OPHTHALMOLOGICAL FINDINGS

Corneae On the nasal side of both corneae some streaks were to be seen, radially arranged, as if belonging to a vortex, of which only the nasal part was present.

SKIN

There were no lesions. The biopsy was positive for lipid staining.

Case 12, *a female aged* 39; B, IV, 2.

The patient's father (B, III, 2) died at the age of 45 from renal complications of angiokeratoma.

OPHTHALMOLOGICAL FINDINGS

Corneae Vortex opacity.

SKIN

There were no lesions. The biopsy was positive for lipid staining.

Case 13, *a boy aged* 17, son of Case 12; B, V, 3.

OPHTHALMOLOGICAL FINDINGS

Corneae The vortex opacity was present in both corneae, consisting of a pattern of very delicate streaks.

Fundi No abnormality was to be seen.

SKIN

There were a very few skin lesions. The biopsy was positive for lipid staining.

Family F

Case 14, *a female aged* 24; F, II, 1. The father of this patient died at the age of 36 from renal failure.

OPHTHALMOLOGICAL FINDINGS

Corneae There was a typical vortex in both corneae, more pronounced on the right side.

SKIN

There were very few lesions. The biopsy was positive for lipid staining.

Case 15, *a female aged* 23, sister of Case 14; F, II, 2.

OPHTHALMOLOGICAL FINDINGS

Conjunctiva On both sides there were temporally distended saccular vessels.

Corneae Very distinct vortical opacities in both corneae.

SKIN

There were occasional lesions. The biopsy was positive for lipid staining.

Case 16, *a female aged* 18, sister of Case 14; F, II, 3.

OPHTHALMOLOGICAL FINDINGS

Corneae There were temporal and nasal whirl streaks in both corneae.

SKIN

There were occasional lesions. The biopsy was positive for lipid staining.

Case 17, *a female aged* 15, sister of Case 14; F, II, 4.

OPHTHALMOLOGICAL FINDINGS

Corneae There were very distinct vortex opacities in both eyes.

SKIN

There were no lesions. The biopsy was positive for lipid staining.

In patients F, I, 3; II, 6 and 7, diagnosis was made by skin biopsies. No opthalmological investigation was possible, and general investigation was negative.

Case 18, *a man aged* 34, not belonging to the two sibships described above.

OPHTHALMOLOGICAL FINDINGS

Conjunctiva The bulbar conjunctiva in both eyes showed small saccular distensions.

Corneae Small streaks of superficial opacity were seen; these were not, however, of the typical vortex pattern.

Fundi The discs, which had been choked on both sides in the course of the disease, were now sharply outlined. The arteries showed thick walls and narrowed lumina. There was a marked tortuosity of the branches of the inferior temporal vein of the right eye and of the superior temporal vein of the left eye.

GENERAL EXAMINATION

The skin showed the typical picture of angiokeratoma: most lesions were localized in the lower lumbar and abdominal region.

SKIN

The biopsy was positive for lipid staining.

In this patient the complaints started at the age of 30, with *neurological* symptoms: chiefly flaccid paresis of both legs. Afterwards he developed transient paralysis of the left oculomotor nerve, and 6 months later, a sudden partial transverse lesion at the 10th thoracic level with severe paresis of both legs. There was a horizontal nystagmus. Sensation for all modalities was disturbed below T.10. This last symptom disappeared in one day, the paresis decreasing gradually. During this time the optic discs were choked on both sides. In the cerebrospinal fluid the cell count was slightly raised. Pandy reaction positive, albumin 65 mg./100 ml., globulin 25 mg./100 ml., glucose 46 mg./100 ml. Colloidal reactions normal.

Although the disturbances of the central nervous system had much in common with those of disseminated sclerosis, they were interpreted as symptoms of the storage disease.

Comment

Our series of patients with angiokeratoma consists of seven male and eleven female patients. In the males skin symptoms were present in four cases, the youngest being 15 years. The three patients without skin symptoms were younger. Skin lesions in female patients were slight in five and absent in six cases.

Ophthalmological findings consisted of abnormalities of the conjunctival vessels (7 patients) or segmental dilatation or tortuosities of the retinal vessels (6 cases). No abnormalities of the lens, as mentioned by Spaeth and Frost (1965) were found in our patients. *Corneal lesions of the typical vortex character were present in all patients.*

The corneal findings have to be differentiated from:

(*a*) Chloroquine keratopathy, which can show the same whirlform opacities.

(*b*) The hereditary whirlform corneal dystrophy of Fleischer (1910) and Gruber (1946a, b).

Dominant heredity was stressed by Denden (1964), who described two cases, mother and daughter, while thirteen relatives showed no abnormality. Angiokeratoma in these cases cannot be entirely ruled out, because no relatives of the father (grandfather) on the parental side were investigated. Franceschetti (1968) discovered typical Fabry patients in Gruber's cornea verticillata family.

The complete accordance between the corneal findings and skin biopsies in our series is the most important finding. The detection of female carriers at an early age is imperative for eugenic reasons. Slit-lamp examination of the cornea, apart from biopsy, can thus lead to the diagnosis of angiokeratoma.

Summary

A description is given of the ophthalmological and general findings in eighteen patients with angiokeratoma. In all patients skin biopsy was positive. Some showed typical vascular anomalies in conjunctiva and retina. One had severe symptoms of the central nervous system. Typical corneal opacities were present in all cases.

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Pseudo-capsular exfoliation in the Bantu of South Africa

I. Early or pre-granular clinical stage

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The first comprehensive clinical description of pseudo-capsular exfoliation of the lens was published by Vogt (1923, 1925) under the name "superficial exfoliation of the anterior capsule of the lens."

The appearance is described as a deposit of granular material likened to hoar frost or coarse white powder occurring on the anterior lens capsule, pupil margin, zonule, ciliary body, and persistent pupillary membrane, in the anterior chamber angle, and floating free in the aqueous. Pigmentary disturbances occur. Free pigment is often seen in the aqueous and a transient pigment cloud may be seen in the anterior chamber after dilatation of the pupil. Deposition of pigment on the trabeculae produces a dense band seen gonioscopically. Sampaolesi (1959) and Tosi (1964) considered that a pigmented line lying on the corneal side of Schwalbe's line was a very early sign of pseudo-exfoliation.

In the early stages the changes are confined to the anterior lens capsule and occur in two zones. A central zone, absent in 18 per cent. of cases (Tarkannen, 1962) corresponds to the pupillary aperture, it has a matt homogeneous appearance and may be missed unless the pupil is dilated, revealing a distinct edge with or without a few larger granular deposits. The peripheral zone, which is always present, is more distinct. It varies in width and may extend to the zonules. The outer margin has a radial pattern and the inner edge is sharply delineated. This deposit is granular. The intermediate area is clear but may be bridged by isolated deposits or by a continuous sheet. Gifford (1958) believed that the earliest change might be the formation of a continuous sheet of material which broke down in the intermediate area to produce the two distinct zones.

Pseudo-capsular exfoliation is a chronic disease and has a slow and insidious beginning which is difficult to recognize clinically. Early diagnosis depends upon adequate conditions of examination with pupils dilated, using a slit lamp in a darkened room. A further requirement is an examiner who is aware of, and interested in, the condition (Aasved, 1969).

Such a condition may be expected to be diagnosed more frequently at an advanced stage, and it is said to be a disease of old age, average 69·4 years in 418 cases (Tarkannen, 1962). Only eight cases under 50 years of age have been described (Trantas, 1929; Hørven, 1935; Gradle and Sugar, 1940; Gifford, 1957; Joannides, Katsourakis, and Velissaropoulos, 1961; Tarkannen, 1962); the two youngest subjects were aged 31 and 35 (Hørven and Hutchinson, 1967). Early cases of pseudocapsular exfoliation may be detected in mass surveys, but the pupils are seldom dilated; surveys to detect pseudo-capsular exfoliation are generally confined to elderly age groups as in old peoples' homes where the disease is likely to be already advanced.

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It is surprising that pseudo-capsular exfoliation, even in the early stages, should spring suddenly into being as an obvious granular deposit. If deposited as granules of this size it should be detectable elsewhere and if it arises slowly *in situ*, either as minute granules or in a pre-granular stage, it should be detectable in younger subjects by careful observation.

This paper presents observations made during a glaucoma population study (Bartholomew, 1971). Pseudo-capsular exfoliation was especially looked for under favourable conditions and it is believed to have been detected at a very early stage. The clinical appearances are described and the evidence leading to this conclusion is presented and discussed.

Material and methods

In a population study undertaken among the Pondos, a tribe of the Cape Nguni-speaking Bantu of South Africa (Fig. 1), 2,584 persons over the age of 30 years were examined. The examination included biomicroscopy, using a Haag-Streit 900 slit lamp, in suitably darkened rooms, the pupils being dilated in all cases.

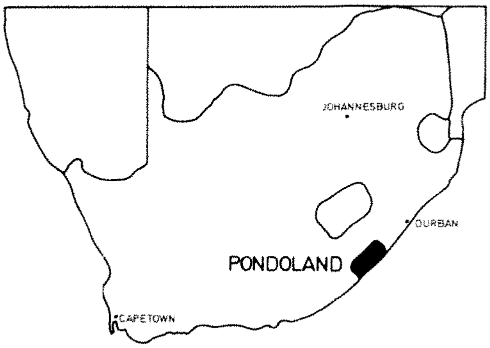

FIG. 1 *Map of South Africa, showing position of Pondoland*

The generally accepted changes of pseudo-capsular exfoliation are described as granular. The early changes detected in the survey are described as pre-granular.

Results

Table I shows the population sample for men and women in 10-year age groups. Fig. 2 (opposite) shows the percentage of granular and pre-granular psuedo-capsular exfoliation by 10-year age groups for men, women, and all cases together. Table II shows the total number of cases and compares the unilateral and bilateral occurrence of granular and pre-granular exfoliation. Table III (opposite) shows cases of particular interest.

Table I *Population sample by age and sex*

Age group (yrs)	*Male*	*Female*	*Total*
30—39	67	90	157
40—49	453	461	914
50—59	338	321	659
60—69	234	315	549
70+	155	150	305
Total	1,247	1,337	2,584

Table II *Analysis of stage of disease*

Side	*Unilateral*	*Bilateral*	*Totals*
Pre-granular	23	53	76
Granular	50	82	132
Total	73	135	208

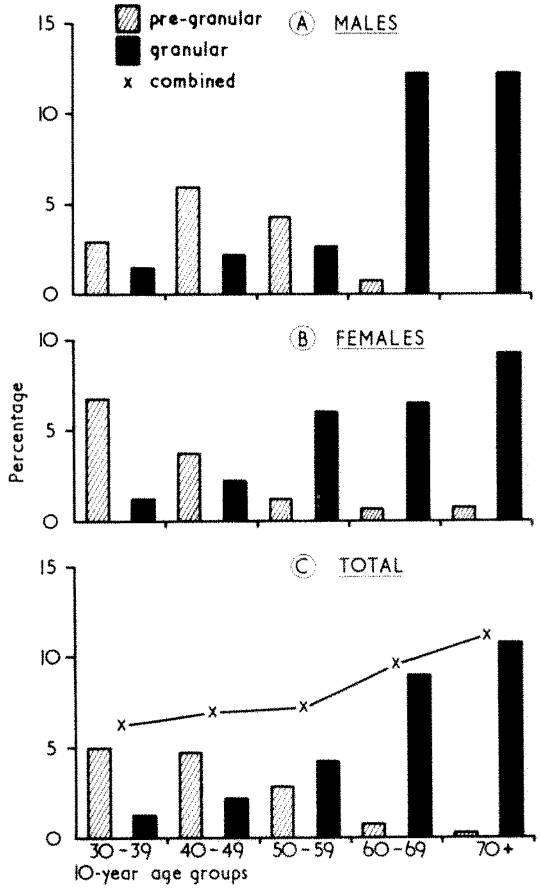

FIG. 2 *Percentage of granular and pre-granular pseudo-capsular exfoliation, by 10-year age groups*

Table III *Cases of particular interest*

Type of case	*No. of cases*
Granular and pre-granular in the same eye	1
Granular in one eye, pre-granular in the other	5
Pre-granular with a pigment cloud	4

CLINICAL APPEARANCE OF THE PRE-GRANULAR STAGE

A gradual progression could be traced from the very earliest to the full picture of pseudo-capsular exfoliation. It is convenient to describe this in stages (Figs 3, 4, 5, 6, overleaf).

In Stage 1 (Fig. 3), greyish radial non-granular striae are visible on the mid-third of the anterior capsular surface, entirely behind the iris. The striae are thin and slightly fusiform, vary a little in length, and are evenly distributed in all quadrants. They number some eighty in all.

The striae are difficult to see. They are most easily seen when a 0·5 mm. width slit beam is focused on the lens surface at an angle of 45° and the whole slit lamp is traversed from side to side. With diffuse illumination the striae tend to disappear and with static

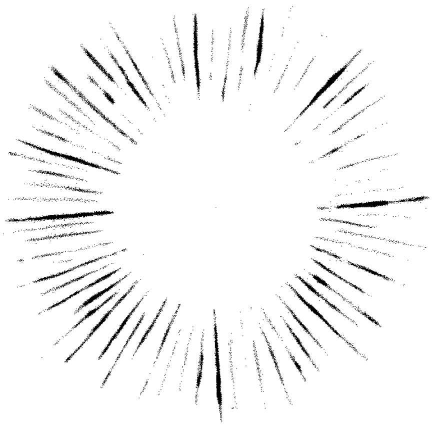

FIG. 3 *Pre-granular pseudo-capsular exfoliation. Stage* 1

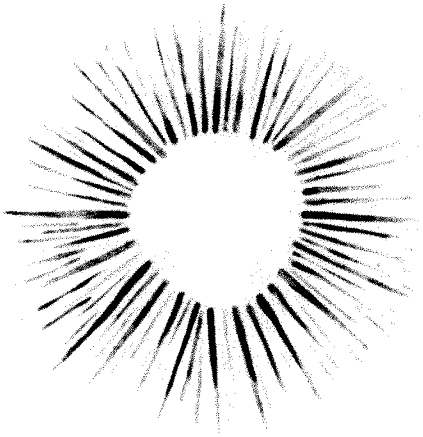

FIG. 4 *Pre-granular pseudo-capsular exfoliation. Stage* 2

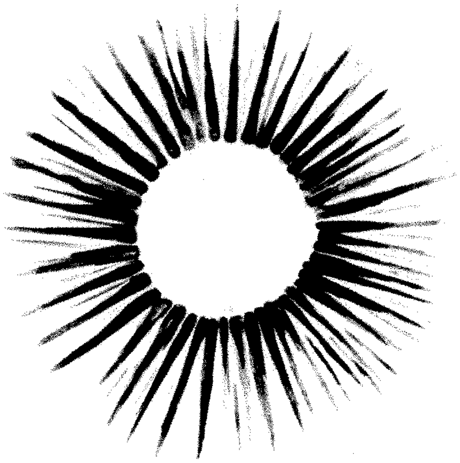

FIG. 5 *Pre-granular pseudo-capsular exfoliation. Stage* 3

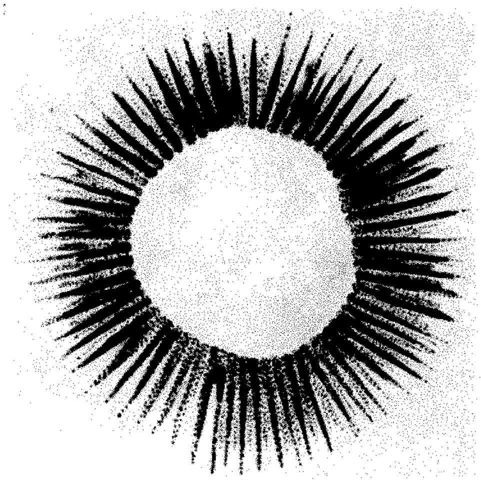

FIG. 6 *Granular pseudo-capsular exfoliation. Stage* 4

illumination the lines are easily missed. Only a segment of each stria can be seen in this way at any time.

On occasion the appearance of the striae is so faint as to be almost imagined, but it grades continuously into Stage 2 (Fig. 4) where they are more easily seen. They become slightly broader and thus lie closer together. The outer ends become a little longer while the inner ends become blunted and broader.

In Stage 3 (Fig. 5), the striae broaden and the blunted inner ends begin to touch one another, thus forming a continuous dentate line. No visible granular deposits occur (with 25 times magnification). With the addition of fine granular deposits, this stage merges into Stage 4 (Fig. 6) which becomes the generally accepted early stage of pseudo-capsular exfoliation.

No central deposit was noticed in Stages 1 or 2 but some cases in Stage 3 gave the impression of a faint greyish matt deposit; lacking the visual contrast of the striae and their background this could not be confirmed.

Discussion

Evidence that this appearance was in fact an early stage of pseudo-capsular exfoliation came from a consideration of the morphology of the deposits and of certain individual cases, the prevalence of granular and pre-granular stages in the population sample, and their unilateral or bilateral occurrence. Other causes which might produce this appearance were considered.

The morphological resemblance between pre-granular and granular pseudo-capsular exfoliation is strong. The radial pattern is similar, each having some eighty lines. This equals the number of structural folds on the posterior iris surface which may play some part in the production of the radial pattern.

Movement of the iris and pupillary margin against the capsule is responsible for the width of the outer band. In Stage 1, the striae are too peripheral to be affected by the iris and the inner ends of the striae remain pointed. As the striae lengthen centrally they come within range of the iris effect and the pointed inner ends become blunted (Stages 2 and 3).

A 40-year-old man presented one eye with the appearance shown in Fig. 7. One quadrant showed definite granular pseudo-capsular exfoliation which merged in the opposite quadrant to the radial striae of Stage 1. His other eye showed striae in Stage 1. This case was unusual as progression in an eye is usually radially symmetrical in the absence of iris abnormalities. This case provided a major clue in confirming that the radial striae were due to pseudo-capsular exfoliation.

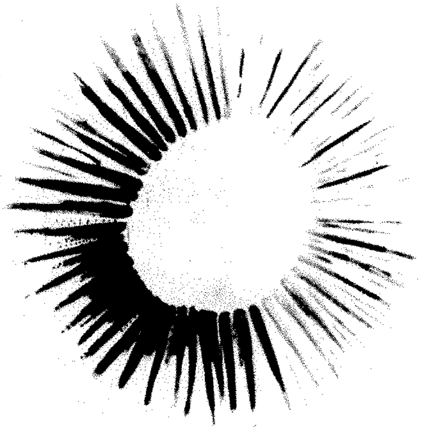

FIG. 7 *40-year-old male. Pre-granular and granular pseudo-capsular exfoliation in the same eye*

The association of granular pseudo-capsular exfoliation in one eye with pre-granular pseudo-capsular exfoliation in the other was seen in five more cases. This may be due to chance, but is readily explained by the fact that pseudo-capsular exfoliation is commonly bilateral.

Four patients with pre-granular pseudo-capsular exfoliation produced a pigment cloud in the anterior chamber after dilatation of the pupil. This is a characteristic feature of granular pseudo-capsular exfoliation. Pigmentary disturbances are a common senile change; their occurrence in such young cases favours a generalized ischaemic process rather than a localized lens abnormality as a cause for pseudo-capsular exfoliation.

These ten cases strongly suggest on clinical grounds that the pre-granular appearance is an early stage of pseudo-capsular exfoliation.

The prevalence of the pre-granular stage in the sample of the population (Table I and Fig. 2) is highest in the 30 to 39-year age group (5·1 per cent.) and falls with increasing age to the lowest level in the over 70-year age group, in which only one case was seen (0·3 per cent.).

The prevalence of granular pseudo-capsular exfoliation is lowest in the 30 to 39-year age group (1·3 per cent.) and rises steadily through the age groups to its highest level in the over 70-year age group (10·9 per cent.). The falling prevalence of pre-granular pseudo-capsular exfoliation can be explained if these cases steadily progress and become granular until, in the over 70-year age group, nearly all have become granular.

Granular pseudo-capsular exfoliation is unilateral in 45 to 48 per cent of cases (Gifford, 1957; Tarkannen, 1962). In the population studied, 132 cases were seen, fifty (38 per cent.) unilateral, and 82 (62 per cent.) bilateral, 76 pre-granular cases were seen: 23 (31 per cent.) were unilateral and 53 (69 per cent.) were bilateral. This again suggests that the two groups are stages in the same entity.

Pseudo-capsular exfoliation may be confused with true exfoliation of the lens capsule, remnants of exudation following iritis, iris atrophy, and heterochromic cyclitis. None of these conditions were seen in any of these cases. Retro-iridal pigmented lines and stripes (Berliner, 1949), which have a radial pattern on the anterior lens surface, are thin pigmented lines and are readily recognizable. Superficial anterior grey radial striae (Rehsteiner and Schläpfer, 1930) in description and illustration very closely resemble the appearance described here, although localized as being subcapsular (Vogt, 1931). They were seen in over half of 59 glass blowers and one-fifth of persons not exposed to infra-red irradiation. Abramowicz (1933) reported these striae in 90 per cent. of 240 persons with no occupational exposure to heat. Berliner (1949) concluded that the significance of these radiating structures was not entirely understood. The observations presented here suggest that anterior grey radial striae and the appearance described may be the same and that both may be due to pseudo-capsular exfoliation.

From these observations it is concluded that the pre-granular stage is the earliest sign of pseudo-capsular exfoliation yet described, and that it occurs commonly between 30 and 50 years.

Further studies are in progress to obtain histological material of the pre-granular stage and to investigate the relationship of granular and pre-granular exfoliation to intra-ocular pressure.

Summary

(1) Pseudo-capsular exfoliation has been detected at a very early stage, termed pre-granular, during a population study among Pondos of South Africa.

(2) It occurred in 5·1 per cent. in persons between the ages of 30 and 39 years of age and fell to 0·3 per cent. in persons over the age of 70 years.

(3) The clinical appearances are described. Morphological, clinical, and statistical evidence that this appearance is pseudocapsular exfoliation is presented and discussed.

(4) This appearance may be the same as anterior grey radial striae.

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Role of serum protein in the ocular manifestations of vitamin A deficiency

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The ocular lesions of vitamin A deficiency, in order of severity, are brown pigmentation of the conjunctiva, defective dark adaptation (clinically manifested as night blindness), Bitot's spot, xerophthalmia, and keratomalacia. The first four conditions are due to the mild chronic form of vitamin A deficiency and the last to the severe acute form.

Night blindness, xerophthalmia, Bitot's spot, and keratomalacia were identified and treated with liver and liver oil before the discovery of the vitamins, but the pathogenesis of these ocular manifestations of vitamin A deficiency are not yet known.

Supplementary protein in the diet causes early and complete disappearance of Bitot's spot and xerophthalmia (Yourish, 1953; Vaughan, 1954; Reddy, 1965; Gupta, Dhir, and Agarwal, 1968). This may be due to an interrelation of the metabolic functions of protein and vitamin A, and the present study seeks to elucidate this relationship.

Materials and methods

Four groups of children aged 1 to 8 years, who were affected by keratomalacia, xerosis, Bitot's spot, and xerosis with Bitot's spot, were admitted to the Eye Ward of Gauhati Medical College Hospital. A complete nutritional and clinical examination, with estimation of serum vitamin A, total serum protein, serum albumin, and serum globulin was carried out.

The children received the standard hospital diet supplemented with a single mega dose of vitamin A (100,000 I.U. – Arovit, Roche) as recommended by the Indian Council of Medical Research (1967) and 1·5 g. milk protein (Casilan) per kg. body weight daily for 15 days, after which the examination was repeated.

Children with no signs of malnutrition were used as a control group and were treated and examined in the same way.

Serum vitamin A was estimated by the method of Kaser and Stekol (1943), using a Klett-Semmerson photoelectric colorimeter. Total serum protein, serum albumin, and serum globulin were estimated by the method of Wu (1920, 1922).

Results

CONTROLS (Table I, opposite). After treatment there was no significant increase in the mean values . The mean total serum protein was raised from 7·31 to 7·63 g/100 ml. and the serum vitamin A rose by 11·8 per cent. The albumin/globulin ratio fell from 2·12 to 2·08 (Table II, overleaf).

KERATOMALACIA (Table I) The mean serum vitamin A level increased two-fold after treatment. The total serum protein in this group varied from 4·26 to 7·60 g./100 ml. (mean 5·82 g/.100 ml.). Along with the low serum protein level, the albumin/globulin

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Table I *Total serum protein, serum albumin, serum globulin, and serum vitamin A in eight normal healthy children, eleven with keratomalacia, six with xerosis, six with Bitot's spot, and six with xerosis and Bitot's spot before and after treatment.*

Diagnosis	*Case No.*	*Age (yrs)*	*Sex*	*Total protein (g./100 ml.)*		*Serum albumin (g./100 ml.)*		*Serum globulin (g./100 ml.)*		*Serum vitamin A (µg./100 ml.)*	
				Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
Control	1	1	M	7·80	7·80	5·44	5·98	1·90	1·82	56	60
	2	5	M	7·56	7·55	5·94	4·44	1·62	3·21	52	64
	3	3	M	5·80	7·85	3·80	6·16	2·00	1·69	60	66
	4	3½	F	7·50	7·80	4·50	5·62	3·00	2·18	50	66
	5	8	M	7·20	7·50	4·50	4·50	2·70	3·00	52	58
	6	6	F	7·65	7·65	5·25	5·05	2·40	2·60	60	62
	7	4	M	7·75	7·67	5·20	4·65	2·55	3·02	58	60
	8	2½	M	7·25	7·25	4·85	4·85	2·40	2·40	50	54
	Mean			7·31	7·63	4·93	5·16	2·32	2·49	34·75	61·25
Kerato-malacia	1	4	M	7·02	7·56	3·80	5·08	3·22	2·48	24	60
	2	8	M	6·50	8·52	4·25	4·90	2·25	3·62	10	38
	3	3	M	4·70	6·78	3·00	4·64	1·71	2·14	28	48
	4	2½	M	5·96	8·80	2·95	5·04	3·01	3·76	16	42
	5	6	M	5·06	7·28	3·32	4·74	1·74	2·54	23	52
	6	6	M	7·40	7·52	4·52	4·74	2·88	2·78	23	54
	7	8	M	5·64	7·28	2·00	3·48	3·64	3·80	48	65
	8	5	M	4·62	6·35	2·00	4·41	2·26	1·94	20	44
	9	6	F	6·30	7·80	2·20	4·39	4·10	3·41	23	52
	10	8	M	7·60	7·78	4·00	4·48	3·60	3·30	40	65
	11	8	F	4·71	6·78	3·60	4·64	1·71	2·14	34	60
	Mean			5·82	2·20	3·25	4·59	2·73	2·90	26·27	52·72
Xerosis	1	6	M	6·35	6·77	1·87	3·24	4·48	3·53	44	50
	2	5	F	7·01	7·20	5·32	5·98	1·69	1·22	34	49
	3	6	F	5·89	6·80	3·48	4·25	2·41	2·55	56	65
	4	4	F	6·82	6·92	5·20	5·28	1·62	1·64	52	60
	5	1½	M	6·60	7·29	2·60	5·98	4·00	2·31	46	50
	6	3	F	6·10	6·92	3·10	5·28	3·00	1·64	40	48
	Mean			6·46	6·98	3·59	5·00	2·87	2·15	45·33	53·67
Bitot's spot	1	3½	M	4·78	7·02	3·58	5·28	1·20	1·74	20	52
	2	5	F	5·20	7·02	3·80	5·21	1·40	1·81	40	56
	3	4	F	5·30	6·40	2·84	4·20	2·46	2·20	24	44
	4	4	M	6·40	7·02	3·10	5·21	3·30	1·81	40	56
	5	3	M	5·70	6·80	2·90	4·25	2·80	2·55	26	44
	6	1½	M	4·72	6·90	3·20	4·52	1·52	2·38	22	40
	Mean			3·35	6·86	3·23	4·77	2·11	2·08	28·66	49·00
Xerosis and Bitot's spot	1	6	M	6·03	7·28	4·02	4·44	2·01	2·84	30	52
	2	3	M	6·40	7·48	4·28	5·56	2·12	1·92	40	50
	3	2½	M	6·56	7·56	4·45	5·48	2·11	2·08	34	54
	4	5½	M	7·28	7·92	4·44	5·25	2·84	2·67	28	58
	5	8	M	6·25	7·28	4·20	4·62	2·05	2·66	40	57
	Mean			6·50	6·90	4·28	5·07	2·23	2·43	34·40	54·20

ratio was greatly altered even in cases in which the total serum protein was within the normal range (Cases 1, 2, 10). After treatment the mean serum protein level was raised to 7·20 g./100 ml. and the albumin/globulin ratio improved from 1·34 to 1·60 (Table II).

Table II *Albumin/globulin ratio in different groups of cases before and after treatment*

Group	*No. of cases*	*Albumin/globulin ratio*	
		Before	*After*
Control	8	2 12	2·08
Keratomalacia	11	1·34	1·60
Xerosis	6	1·25	2·57
Bitot's spot	6	1·53	2·24
Xerosis with Bitot's spot	6	1·92	2·09

XEROSIS (Table I) The mean serum vitamin A level rose from 45·33 to 53·67 µg./100ml. There was no increase in the total serum protein level. The albumin/globulin ratio improved from 1·25 to 2·57 (Table II).

BITOT'S SPOT (Table I) The mean serum vitamin A level rose from 28·66 to 49·00 µg./100 ml. and the mean serum protein level rose by 28·2 per cent.
The albumin/globulin ratio rose from 1·53 to 2·24 (Table II).

XEROSIS AND BITOT'S SPOT (Table I) There was a significant increase in the serum vitamin A level and, although there was no significant change in the mean serum protein level, the albumin/globulin ratio increased from 1·92 to 2·09 (Table II).

Discussion

McLaren (1964) suggested that the eyes were affected if the serum vitamin A level fell below 20µg./100 ml., but in the present series keratomalacia, xerosis, and Bitot's spot occurred in patients with levels as high as 56 µg./100 ml., suggesting that hypovitaminosis A is not the only aetiological factor in the ocular lesions which accompany malnutrition. Dhir, Gupta, and Agarwal (1968) demonstrated that the administration of vitamin A alone was incapable of curing the ocular lesions of hypovitaminosis A.

Though hypovitaminosis A was not frequently found in the present series, hypoproteinaemia with altered albumin/globulin ratio was noted almost in every case. Similar observations of hypoproteinaemia in cases of keratomalacia and xerophthalmia were made by Yap-Kie-Tiong (1957) and Gopalan, Ventakachalan, and Bhavani (1960). In our cases the serum protein level increased and the albumin/globulin ratio became normal after treatment, with clinical improvement of the ocular lesions.

The importance of giving protein as well as vitamin A in the treatment of hypovitaminosis A has been studied by various workers (Yourish, 1953; Vaughan, 1954; Bagchi, Halder, and Chowdhury, 1959; Reddy, 1965; Gupta and others, 1968). Yap-Kie-Tiong (1956) observed that the serum protein levels were lower in patients with keratomalacia than in those with xerophthalmia, while the concentration of vitamin A was approximately the same. It has also been reported that xerosis, Bitot's spot, and keratomalacia may occur when the serum vitamin A level is normal but the serum protein level is low (Cecil and Loeb, 1951; Sen, 1954; Yap-Kie-Tiong, 1956; Venkataswamy, 1967).

Protein deficiency produces a fatty infiltration of the liver and impairment of the normal functions of the liver cells. As the liver is a vital organ for vitamin A metabolism, protein deficiency prevents the availability of vitamin A to the body. Factors which influence the absorption, biosynthesis, and storage of vitamin A all tend to lower the serum vitamin A level (Abboud, Osman, and Massoud, 1968). Protein deficiency causes the rapid exhaustion of stored vitamin A, the impairment of digestion and malabsorption, and the reduction of power to utilize the small amounts of vitamin A and provitamins (Moore, 1960) which are still available in the body. Our study has shown that where the total serum protein level is low, the serum vitamin A level is also low. It is clear that protein plays a vital role in the prevention of the ocular manifestations of vitamin A deficiency, and that in the treatment of such cases protein and vitamin A should be given together.

Summary

Children with various ocular lesions due to hypovitaminosis A were treated with one mega dose of vitamin A and 1·5 g. milk protein per kg. body weight daily for 15 days. In almost every case the clinical condition improved, and the serum vitamin A and protein concentration and the albumin/globulin ratio became normal. Both protein and vitamin A should be used in the treatment of the ocular manifestations of vitamin A deficiency.

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Visual field analyser and threshold

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The Visual Field Analyser was introduced by Friedmann (1966), and further details of the instrument were published by Bedwell (1967).

The Analyser operates on the principle of multiple stimulus presentation. Two, three, or four stimuli of *equal standard luminance*, are presented simultaneously, the standard luminances being different for different age groups. Stimulus size and stimulus luminance have been selected so that normal subjects of a given age group should see all stimuli presented. This assumes that the given standard stimulus size and luminance is situated *approximately at threshold level*. Visual field investigation is, by definition, the investigation of the topography of the light sensitivity of the eye: that is, the investigation of the differential threshold. The purpose of this investigation was to study the distance between the standard stimulus of the Visual Field Analyser and the threshold.

It is not necessary to carry out the investigation at a standard luminance. As is commonly done in static perimetry, the luminance may be increased from the infraliminal level until the stimuli are observed. This poses the question whether the simultaneously presented stimuli reach the threshold simultaneously, that is at the same luminance, or not. It may be concluded from what is known about the inter-individual difference of the form of the gradients of sensitivity in static perimetry[1] that a simultaneous approach to the threshold is not possible (Harms, 1953; Aulhorn and Harms, 1967; Fankhauser and Schmidt, 1963; Verriest and Israel, 1965; Greve and Wijans, 1971).

Method

21 males between the ages of 20 and 30 years were investigated with the Visual Field Analyser according to the method described previously by Greve (1970). One difference between this method and that described in the Visual Field Analyser instruction book is that a stimulus initially not seen is presented twice more. The stimulus is considered to have been missed if the subject observes it only once out of the three presentations. The stimulus is then presented at a higher luminance. This method prevents false positive results.

All subjects investigated had normal eyes, normal visual acuity, and no history of ocular disease. The investigation commenced from the infraliminal level which was at filter dial 2·8 on our instrument. As soon as the subject saw one or more stimuli, but fewer than the total number presented, he was asked to indicate where these were situated. Stimuli not observed were repeated as described above. In this manner a threshold luminance, expressed as filter dial position, was determined for each of the 46 stimuli.

The positions of the stimuli of the Visual Field Analyser are shown in Fig. 1, and the groups of stimuli presented in Fig. 2.

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[1] In static perimetry the differential light-sensitivity is usually investigated on several locations along one meridian. The results are presented graphically as a curve that indicates the variation of log luminance (threshold-luminance) with retinal location. Such curves show the gradient of sensitivity, *i.e.* the variation of sensitivity with retinal location.

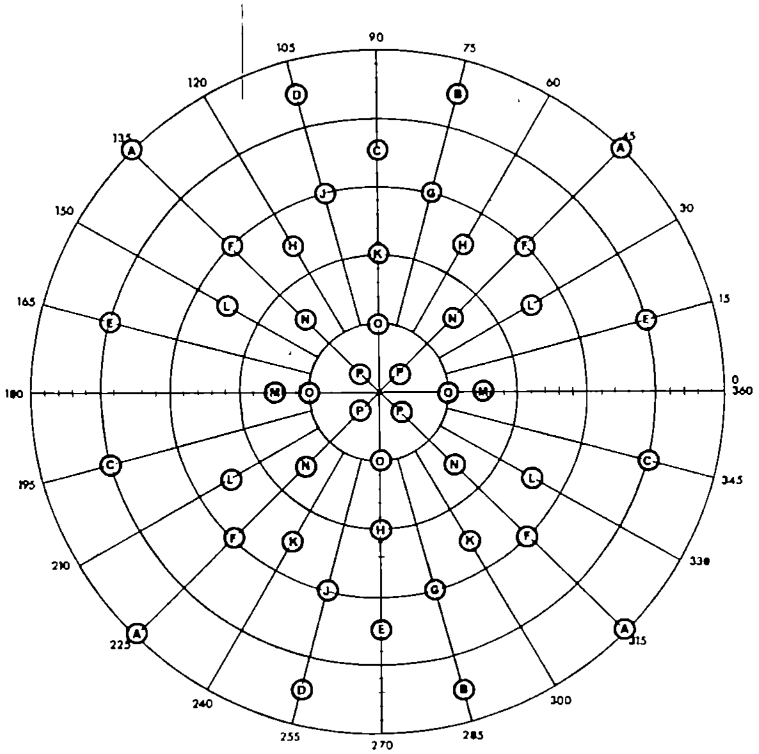

FIG. 1 *Composite chart of the Visual Field Analyser*

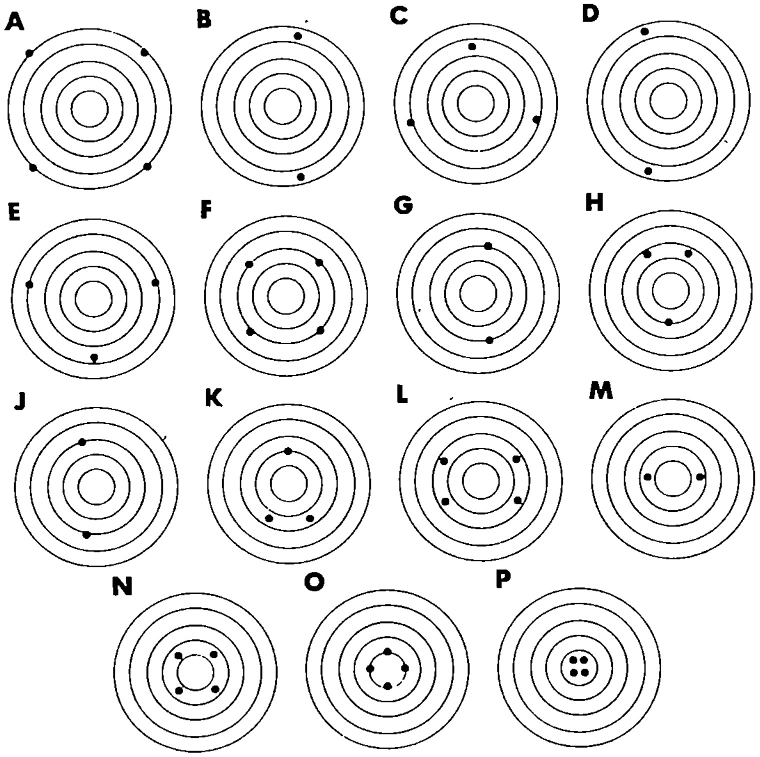

FIG. 2 *Fifteen positions, A to P, on the Visual Field Analyser*

The light-source of the Visual Field Analyser is a Xenon tube. It is difficult to measure the luminance of these short flashes and to express it in customary luminance units. Bedwell (1967) described approximate values for both luminance and duration of flash. The luminance of the flash is reduced by means of Kodak Wratten neutral density filters in logarithmic steps. Each density step reduces the luminance by 0·2 l.u. (logarithmic units). The filter dial positions indicate the number of l.u. by which the original flash luminance has been reduced. A filter dial position of 2.0, for example, indicates that the stimulus luminance has been reduced by 2 l.u., which means that only 1 per cent. of the original luminance comes through. A high filter dial position means a low luminance and a low filter dial position a high luminance.

To avoid the problems of measuring flash tubes we have not indicated the stimulus luminance but instead the filter dial position, which seems to be the most easily understood for practical purposes.

Results

Fig. 3 shows the results for 26 of the 46 stimuli, for four subjects. The location is indicated along the abscissa, and the eccentricity increases from left to right. The filter dial positions are indicated along the ordinate. A straight line indicates simultaneous perception of all stimuli at one filter dial position.

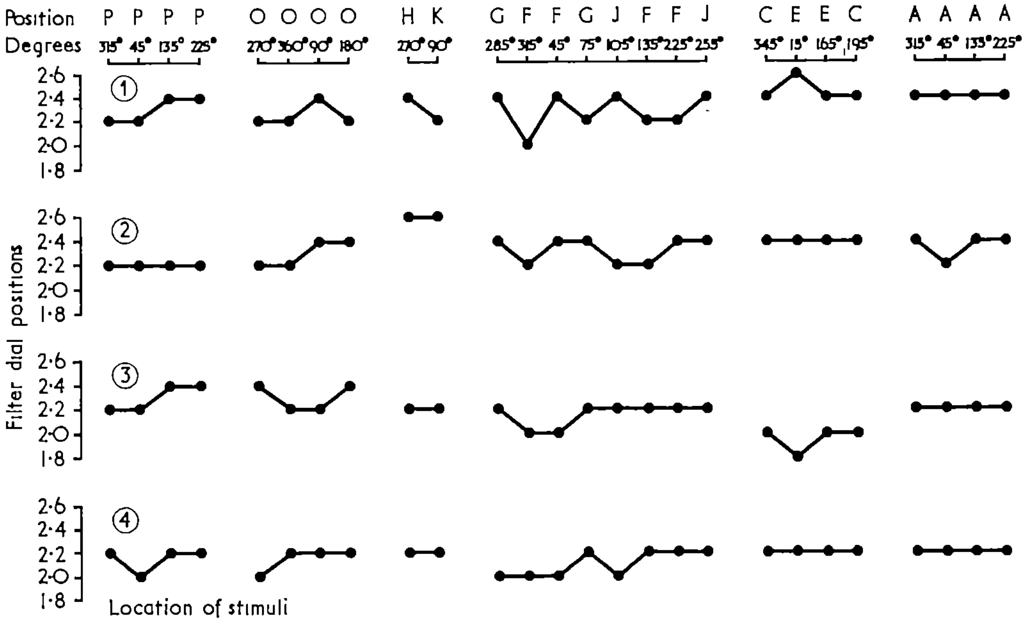

FIG. 3 *Results of 26 stimuli in four subjects*

Table I shows the results obtained from the 21 subjects for 26 stimuli of the Visual Field Analyser. The left-hand column shows the lowest luminance (highest filter dial position) at which subjects could still see one or more stimuli. The right hand column shows the number of subjects who saw these stimuli at the corresponding luminance. Only three subjects observed some stimuli at filter position 2·6; fourteen could observe some stimuli at 2·4, and four needed a filter position of 2·2 to observe some stimuli.

Table II shows that many stimuli were observed at different threshold luminances. The left-hand column shows the greatest differences in threshold-luminance found for each subject (intra-individual difference) expressed in log. units. The right-hand column gives the number of subjects who showed the difference in threshold luminance indicated

Table I

Highest filter dial position	*No. of subjects*
2·6	3
2·4	14
2·2	4
Total	21

Table II

Greatest difference	*No. of subjects*
0·6	3
0·4	6
0·2	11
Total	20

in the left column. Three showed a difference of 0·6 l.u., which was present for only one stimulus in each subject. A difference of 0·4 l.u. was found in six subjects for several stimuli. In half of the subjects a difference of 0·2 l.u. existed.

Discussion

It appears that the standard luminance for subjects up to 40 years of age, that is the filter dial position 2·0 as recommended by Friedmann (1966) and Bedwell (1967), is 0·4 l.u. removed from threshold luminance for fourteen normal subjects. Consequently, it is possible to fail to detect a defect of 0·4 l.u. when using this standard luminance. An example of a 0·4 l.u. defect is given in Fig. 4, which was also investated kinetically with the Goldmann perimeter. This was not a small defect, as the patient had a pituitary tumour.

The difference between the recommended filter dial position and the individual optimum filter dial position can even be greater for the older age groups.

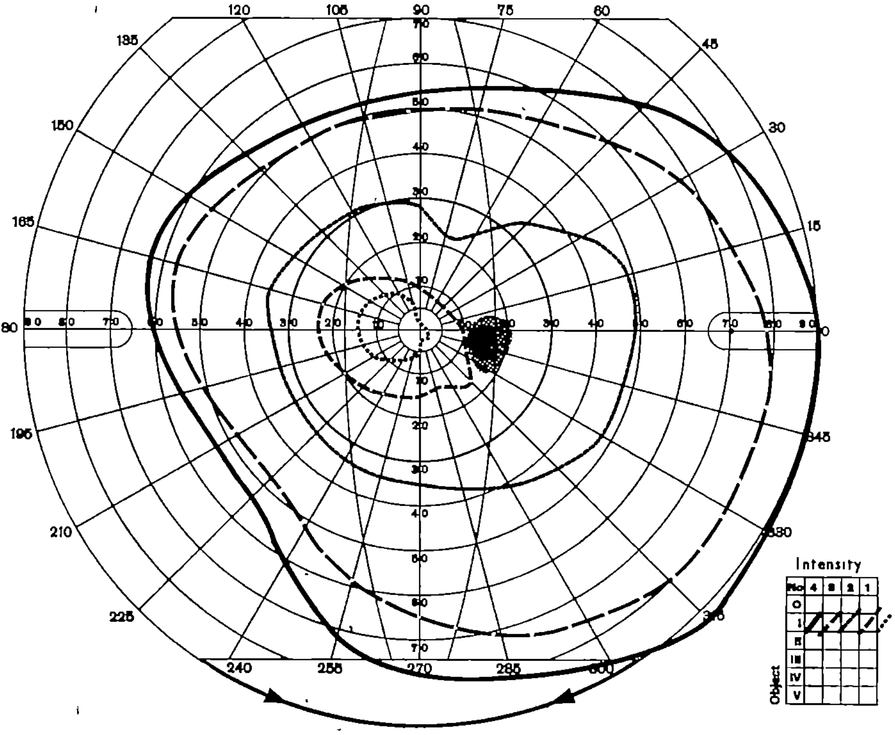

FIG. 4 *Example of a patient with a* 0·4 l.u. *defect due to a pituitary tumour*

One should not forget in interpreting the results that, when all subjects are investigated from the infraliminal level, as is our practice, differences of 0·4 l.u., that is two filter dial steps, may be found even in normal subjects.

This difference may be due to the appreciable individual differences in the gradient of sensitivity, to the interaction of several of the stimuli of a simultaneously presented group, or to an incorrect choice of stimulus size and technical imperfections of the size of the different stimuli.

Apart from the loss of intensity of the stimuli, their *position* is, of course, of importance in interpretation.

We measured the sizes of the different stimuli and found that there are differences between stimuli that ought to have the same diameter. However, these differences are too small to explain the differences that we found in the threshold values.

While the multiple stimulus investigation was carried out, we also investigated the same subjects using a similar single stimulus method.

The differences between the threshold values for the single stimulus method were equal to those for the multiple stimulus method, so that the interaction of stimuli cannot account for the differences.

The cause is more likely to lie in individual departures from the average pattern of gradient of sensitivity which has been investigated by Greve and Wijnans (1971).

Conclusion

The purpose of this paper is to give a warning, *not* against the *use* of the Visual Field Analyser, but against its incorrect and thoughtless use.

We disapprove of the use of a fixed filter dial position except in mass investigations. It is preferable to start the investigation from the infraliminal level.

When interpreting the results one should take into account normal mutual differences of 0·4 l.u. and sometimes even 0·6 l.u. With these provisos the Visual Field Analyser will be found to be a useful instrument for rapid visual field investigation.

Summary

A warning is given against the incorrect use of the Visual Field Analyser. The recommended filter dial positions and the differences in threshold luminance between the various stimuli are discussed.

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Recurrence of proptosis caused by a second orbital tumour of different pathology

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The two following cases are described because, some years after the successful surgical removal of a simple encapsulated orbital tumour, proptosis of the same eye recurred because of a second tumour of different pathology. Such a sequence of events has rarely been reported in the literature.

Case reports

There was no significant family history and no history of trauma or of *x* ray therapy. There were no signs of endocrine disturbances, and no enlargement of the thyroid gland, liver, spleen, or lymph glands. The chest and abdomen revealed no abnormality. The skin did not show *café-au-lait* areas of pigmentation, nodules, or haemangiomata. The temperature, pulse, blood pressure, urine, faeces, blood counts, and bleeding and clotting times were normal. The blood Wassermann reaction, tuberculin test, and Casoni's test for hydatid were negative. The basal metabolic rate, and the ^{131}iodine uptake were normal.

Case 1, a 50-year-old man, complained of left proptosis of 5 years' duration (Fig. 1).

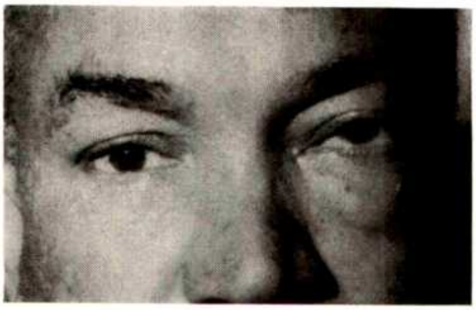

FIG. 1 *Case 1. Left proptosis due to benign haemangioendothelioma in a man aged 50 years.*

EXAMINATION

The right eye was normal with a normal fundus and the visual acuity was 6/9. The left eye showed proptosis forwards and upwards of 22 mm. Hertel (right side 16 mm.) and limitation of ocular movements downwards. The fundus was normal, and the visual acuity 6/18 with no error of refraction. A soft mass was felt between the lower orbital margin and the eye. Skull *x* ray showed no change in the orbits or paranasal sinuses.

TREATMENT

A lower fornix conjunctival incision was made and the tumour was located below and towards the

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inner side of the eye. It was not attached to the optic nerve and was removed easily by blunt little-finger dissection. The tumour was encapsulated and measured 4 × 2 cm. (Fig. 2); it was soft, nodular, and pinkish grey in colour.

(2)

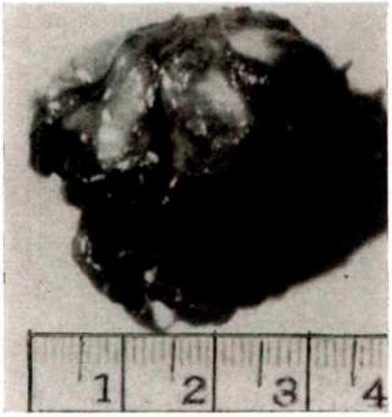
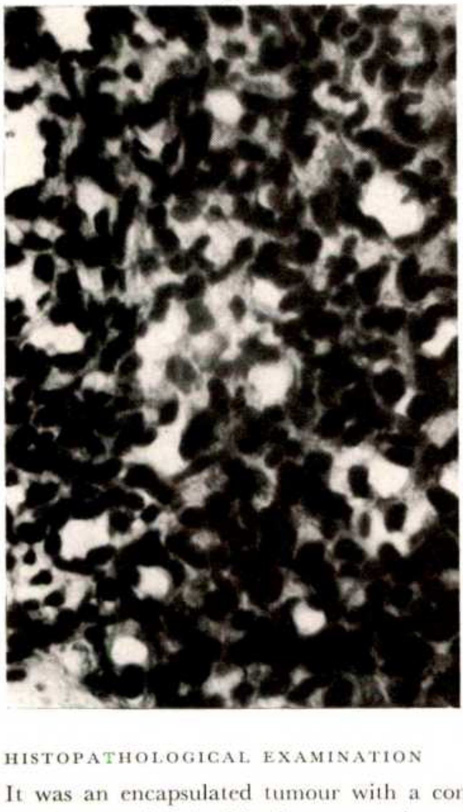


FIG. 2 *Case* 1. *Tumour measuring* 4 × 2 *cm., pink and encapsulated*

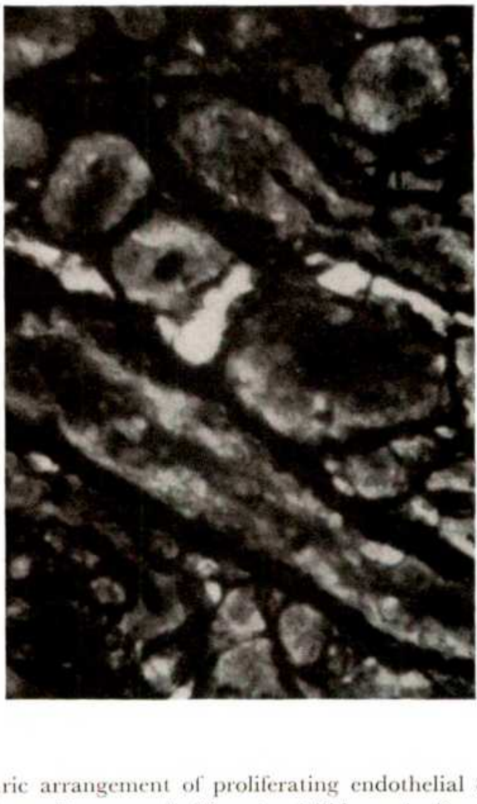
FIG. 3 *Case* 1. *Section of haemangioendothelioma, showing proliferating endothelial cells surrounding clefts and blood spaces.* ×540

FIG. 4 *Case* 1. *Section of haemangioendothelioma, showing endothelial cell proliferation inside neoplastic capillaries. Wilder reticulin stain.* ×540

(3)



(4)



HISTOPATHOLOGICAL EXAMINATION

It was an encapsulated tumour with a concentric arrangement of proliferating endothelial cells mostly around clefts, blood spaces, and neoplastic capillary vessels (Fig. 3). Wilder reticulin stain showed endothelial cell proliferation inside the capillary lumina (Fig. 4).

DIAGNOSIS

Haemangioendothelioma.

PROGRESS

The patient continued in perfect health and with no proptosis for 3 years (Fig. 5).

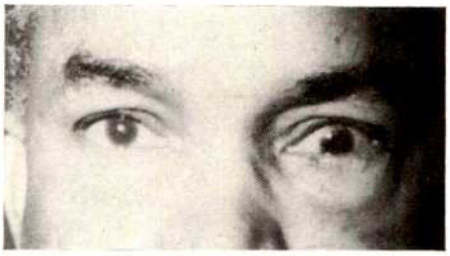


FIG. 5 *Case* 1. *3 years after removal of benign haemangioendothelioma, showing absence of proptosis*

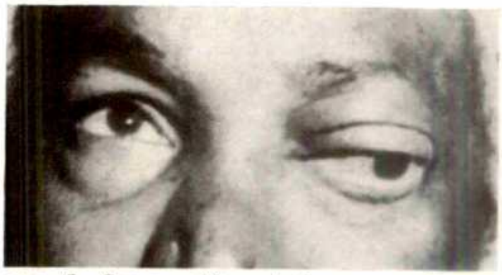


FIG. 6 *Case* 1. *After a further 3 years, there was recurrence of the left proptosis, but this time the cause was a maxillary carcinoma.*

RECURRENCE

After another 3 years there was a recurrence of left proptosis (Fig. 6). The right eye remained normal, and the visual acuity was 6/9. The left eye, which was blind, showed proptosis outwards of 26 mm. (Hertel) with some limitation of ocular movements in all directions. The fundus showed optic atrophy. Skull *x* rays showed some opacity of the left maxillary sinus with destruction of the bony floor of the orbit (Fig. 7). Orbital exploration revealed the extension to the orbit of a maxillary sinus tumour. Histopathological examination of a biopsy of the tumour showed a moderately differentiated squamous cell carcinoma (Fig. 8). Radiotherapy was given but after 2 years the patient died of pneumonia.

(7)

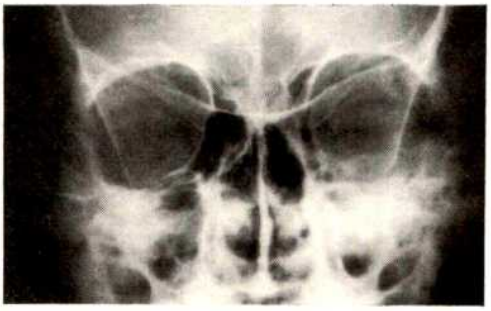


FIG. 7 *Case* 1. *Postero-anterior x-ray of skull, showing opaque left maxillary antrum and destruction of the orbital bony floor by a carcinoma of the maxillary sinus*

(8)

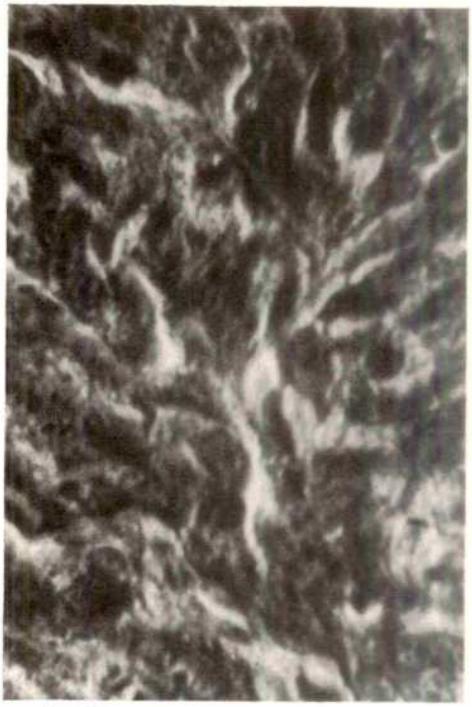


FIG. 8 *Case* 1. *Section of squamous cell carcinoma of left maxillary antrum invading the orbit.* ×540

Case 2, a 45-year-old man, complained of right proptosis of 6 years' duration.

EXAMINATION

The left eye was normal with a normal fundus and a visual acuity of 6/6. The right eye showed proptosis outwards of 20 mm. Hertel (left side 16 mm.) and slight limitation of ocular movement inwards. The fundus was normal, and the visual acuity 6/12. A soft mass was felt between the inner orbital margin and the eye.

TREATMENT

Through an inner fornix conjunctival incision, the tumour was located at the inner side of the eye. It was soft, encapsulated, and red in colour and measured 3 × 2 cm.

HISTOPATHOLOGICAL EXAMINATION

It was an encapsulated cavernous haemangioma (Fig. 9).

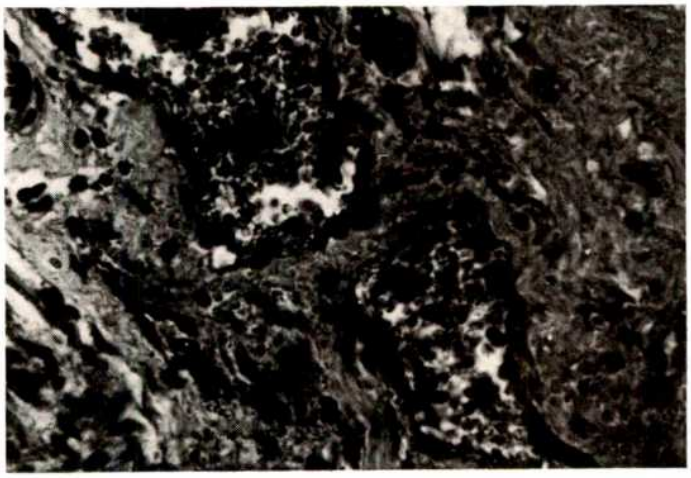


FIG. 9 *Case. 2 Section of cavernous haemangioma removed from right orbit of a man aged 45 years.* ×540

PROGRESS

The patient remained free of proptosis for 4 years.

RECURRENCE

After another 2 years, however, there was a recurrence of the right proptosis (Fig. 10). The left eye was normal, and the visual acuity 6/6. The right eye, which was blind, showed proptosis upwards of 22 mm. Hertel with limitation of ocular movements in all directions. The fundus showed optic atrophy. Skull *x* rays showed opacity of the right maxillary sinus with destruction of the bony floor of the right orbit, which was wider in its vertical diameter (Fig. 11). The blood

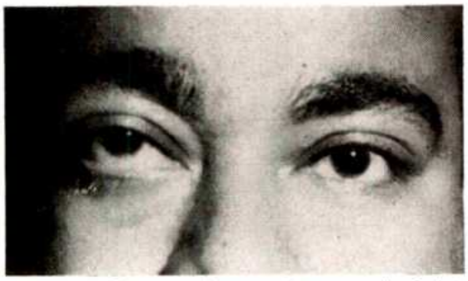


FIG. 10 *Case 2. 6 years after removal of right orbital cavernous haemangioma, there was recurrence of right proptosis which was due to a right maxillary sinus reticulum cell carcinoma*

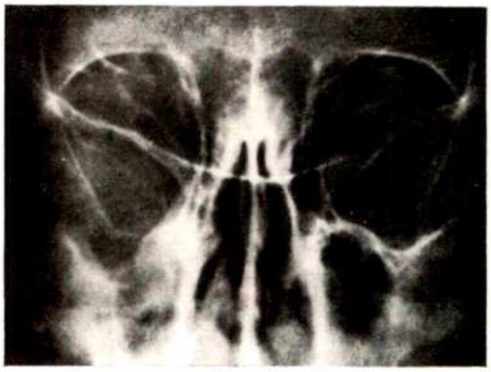
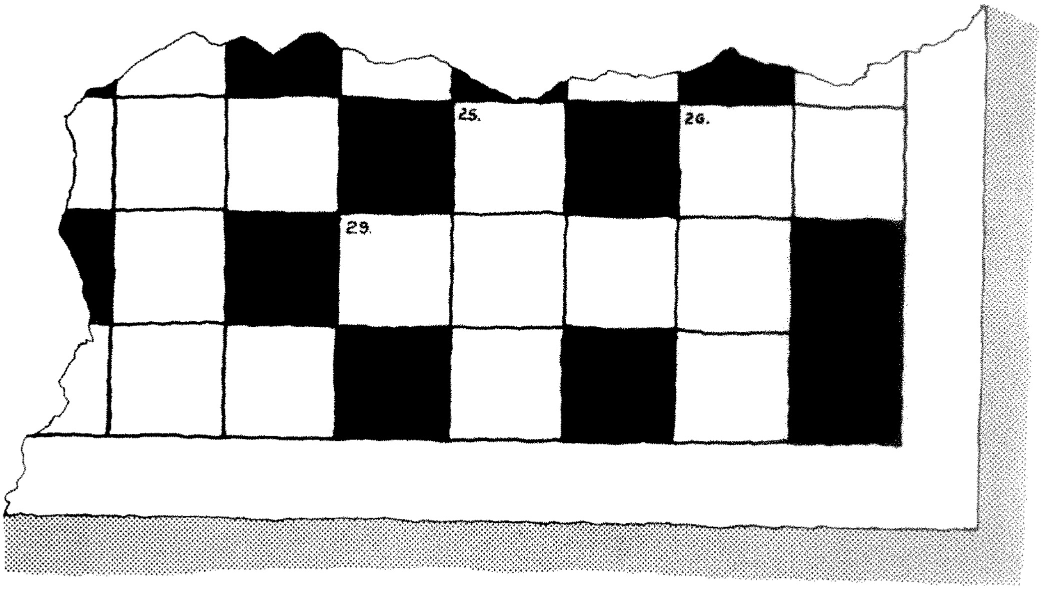


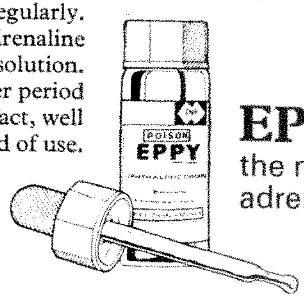
FIG. 11 *Case 2. Postero-anterior x ray view of skull, showing right opaque maxillary antrum and destruction of orbital bony floor by a reticulum cell sarcoma of the maxillary sinus*

29. **Glaucoma?** Change old pennies for new at the centre of an eddy. (4)



The correct solution is ʎddƎ

Eppy is the *only* sting-free adrenaline for use in open-angle and secondary glaucoma. It needs to be applied only once or twice a day, as opposed to the usual four or five times, common to other glaucoma treatments. Here are obvious benefits to the patient, and obvious encouragements to keep up the treatment regularly. Eppy is a long-life l-adrenaline base 1% in an isotonic buffered solution. It remains stable for a longer period than standard adrenaline – in fact, well beyond the recommended period of use. It is made by a patented process and presented in specially formulated 7.5 ml bottles.



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new models now available
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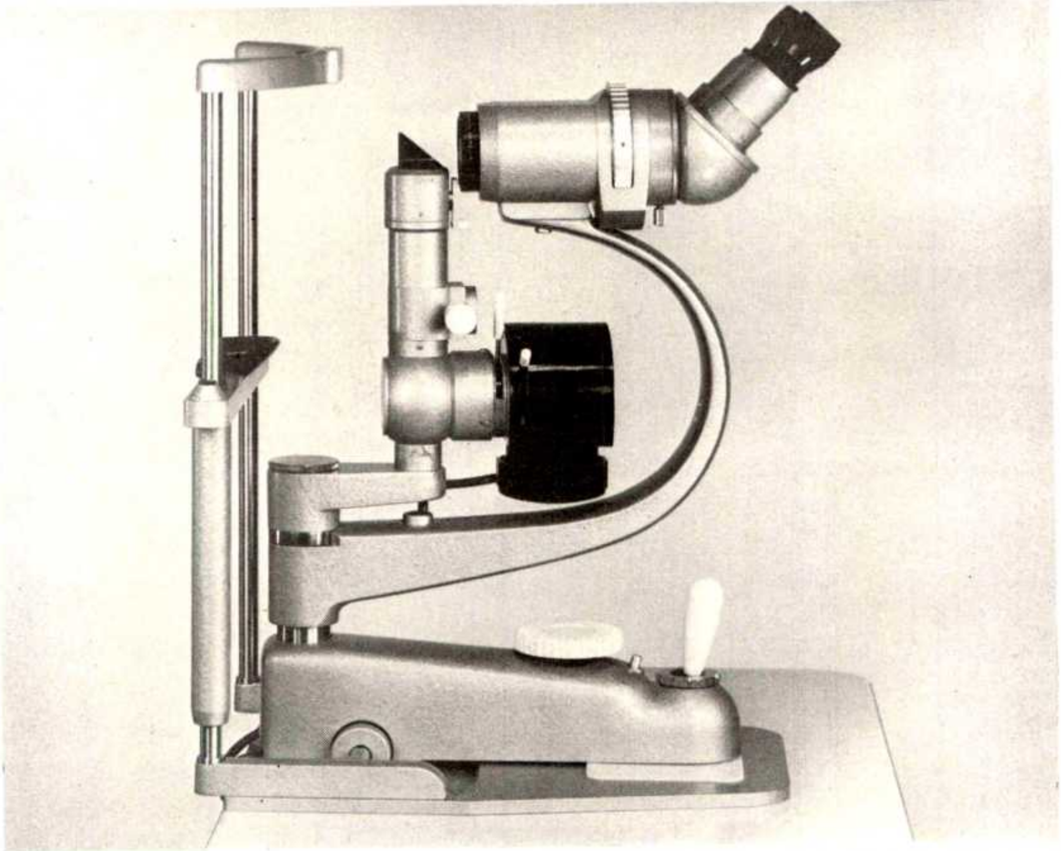

For the first time in slit-lamp microscopy the ophthalmologist has the advantage of the versatility and convenience of a pancratic zoom optical system. Simply by rotating a control a continuous magnification of 7x to 40x is obtained.
3 versions of the slit-lamp 100/16 are now available.
Model PM/M with manual zoom, as illustrated.
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count showed 7 per cent. monocytes. Orbital exploration revealed the extension of a maxillary sinus tumour to the orbit. Histopathological examination of a biopsy of the tumour showed a reticulum cell sarcoma (Fig. 12). Radiotherapy was continued by *x* ray, but 3 years later the patient died of cachexia.

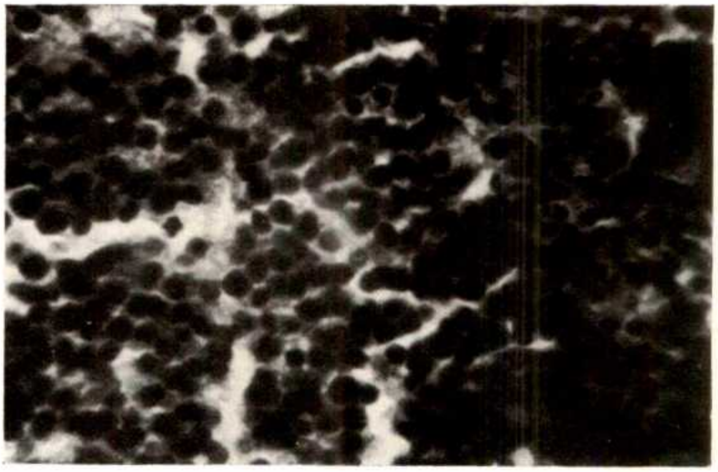


FIG. 12 *Case 2. Section of reticulum cell sarcoma of maxillary sinus invading the orbit.* ×540

Summary

Two very rare cases are reported in which a recurrence of proptosis was due to a second tumour of different pathology.

In the first case the proptosis was originally due to a benign encapsulated haemangio-endothelioma and in the second to a cavernous haemangioma. Some years after successful surgical removal of these benign orbital tumours, proptosis recurred in the same eye. The cause in each patient was a malignant tumour invading the orbit from the maxillary sinus; one was a carcinoma and the other a reticulum cell sarcoma.

Brit. J. Ophthal. (1971) **55**, 714

Ophthalmic lesions due to pine-flower pollen

JOHN SPERO KINNAS
Corinth, Greece

It is well known that allergic manifestations in the eye may be caused by shrubs, grasses, and the seeds and pollen of flowers (Duke-Elder, 1965).

The following observations refer to the pollen of the male flowers of the pine tree. This pollen reaches maturity and is scattered around between mid-March and mid-April, and during this time the eyes of persons in the neighbourhood of the trees may be affected. We have observed nine such cases, two of which are reported in detail below:

DIRECT CONTACT

Case 1, a girl aged 16, working as a goatherd. Her right eye came into direct contact with pollen as a result of pollen-sacs or pine-twigs carrying male flowers striking her face. The subjective symptoms were immediate and intense, causing her to rub the affected eye violently, and when she was seen 14 hours later (Fig. 1) the pollen and pollen-magma were found to have settled as a more or less dense coating around and in the eye. There was a pronounced diffuse oedema, especially of the eye lids.

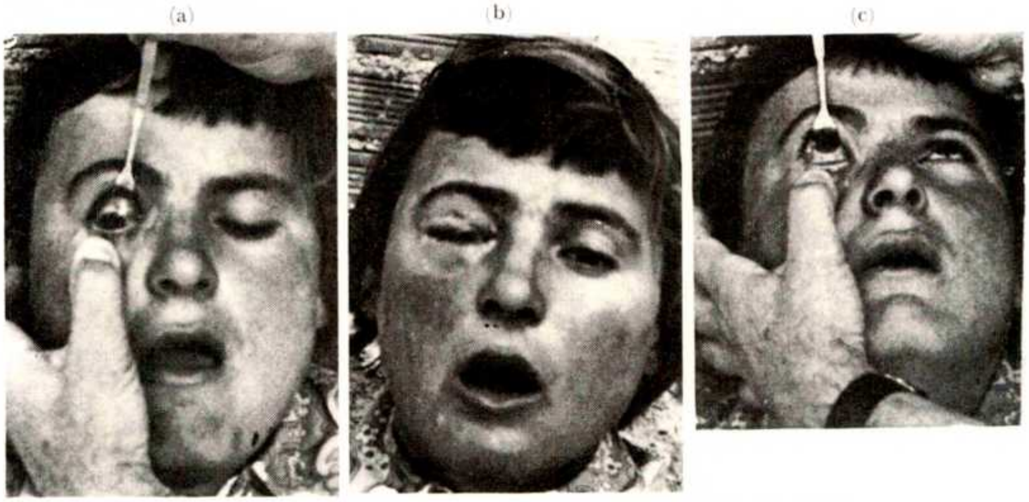


FIGURE *Case 1, showing the results of direct contact with pollen from male pine-tree flowers*

The bulbar conjunctiva in particular showed scattered superficial erosions in the epithelial layer, a marked vascular dilatation, and in places slight ecchymosis.

Biomicroscopy revealed the presence of pale, transparent, papillae of pinhead size, with catarrh and infiltration into the adjacent areas. Some of these papillae showed an epithelial erosion at the apex, mostly with some light-coloured, yellowish-grey spots surrounding the centre. Under 40 magnification such spots could also be discovered on some papillae, where no epithelial erosion had occurred.

Received for publication December 14, 1970
Address for reprints: John Spero Kinnas, Corinth, Greece

Almost the entire corneal surface showed more or less widely dispersed round, whitish, flat maculae as well as linear scratches. The spots were either isolated or merged into irregular patterns.

The epithelial erosions usually extended to Bowman's membrane. At 25 magnification the spots appeared to be granular. After 3 to 5 days the epithelial erosions healed in some parts of the conjunctiva. In the corneae the areas of superficial infiltration were by now confined to the periphery.

On the 5th, 6th, and 7th days the oedema was rapidly disappearing. Ecchymoses were still scattered over almost the entire bulbar conjunctiva, but vasodilatation was receding. The papillae, the epithelial erosions, and the yellowish spots round their apices had mostly disappeared.

The keratitis showed a marked improvement. Between the 8th and 10th day the keratitis had almost entirely cleared. A few sparse papillae still showed, but they had disappeared together with the ecchymoses of the bulbar conjunctiva by about the 20th day.

INDIRECT CONTACT

Case 2, a man aged 35, was out shooting among pine trees, when he accidentally received the contents of some pollen-sacs from a distance of about 8 in. into his right eye. He was seen 10 hours later, when the symptoms were only about half as intense as in Case 1.

Cases 3 to 9. The pollen reached the eye(s), from a distance of 1 to 3 yards or more, and the symptoms were correspondingly milder and more superficial.

Such cases often do not come under ophthalmological observation and treatment as the symptoms clear spontaneously. Treatment consists mainly in the administration of antihistamines and antiallergics.

Discussion

The possibility that the above-mentioned epithelial erosions of the conjunctiva and cornea, as well as the colour of the spots at the apices of the papillae at the sites of epithelial erosion, might be due to mechanical abrasion by the pollen-hairs was ruled out because these hairs when considerably enlarged appear to be only about 1·5 mm. long and are soft and devoid of any barbs or spikes. Moreover, the other parts of the pine-flower, especially the scales, constitute only secondary factors. The pollen is therefore the primary cause of the irritation; the grains contain toxic substances and their action is only to a minor degree, if at all, mechanical. The changes observed must thus be ascribed principally to allergic reactions.

Summary

The pollen of the male flowers of the pine tree cause papillary inflammation of the conjunctiva with characteristic changes in this membrane and in the cornea.

Reference

DUKE-ELDER, S. (1965) "System of Ophthalmology", vol. 8, pt. 1, p. 438. Kimpton, London

Additional bibliography

BOUSSIOU, S. (1968) "Applied Forestry" (in Greek), vol. 1. Athens
MILIARAKIS, S. (1922) "Botany" (in Greek), p. 453. Athens

Brit. J. Ophthal. (1971) 55, 716

Book reviews

The Low Vision Patient. By E. E. FAYE. 1970. Pp. 237, figures, bibl. Grune and Stratton, New York. ($9.75)

This book records the author's experience obtained by dealing with over 6,000 visually handicapped patients at a clinic devoted to the problems of these people organized by the New York Association for the Blind. The term "subnormal vision" is discussed at some length, and much of the book is concerned with refraction and the use of visual aids in those with poor vision. The common causes of subnormal vision are briefly discussed and made more interesting by illustrative case histories.

The section on subnormal vision in the child is by far the best part of the book. The importance of an accurate history from the parents and of a complete general examination of the child is stressed, and there is an excellent discussion on the schooling of such children and their integration into the community.

This is not a technical account, and would be best appreciated by the optician who specializes in low vision aids, by the social worker concerned with the welfare of the blind, and by the physician and paediatrician, although most ophthalmologists would also learn a lot from it. The book should certainly be available to all who deal with visually handicapped people.

Glaucoma Problems. Edited by W. STRAUB. 1971. Pp. 81, 57 figs, bibl. Ophthalmological Library No. 56, Supplement to *Klin. Mbl. Augenheilk.* Enke, Stuttgart. (D.M. 23)

This booklet contains papers read by six authors at an ophthalmological meeting in May, 1970. The light and electron microscopical examinations of Rohen point to the inner wall of the canal of Schlemm as the main site of the outflow resistance of the aqueous in chronic open-angle glaucoma. Sautter, however, localizes the main outflow resistance in the pre-canalicular trabecular network, a view which is supported by the success of goniotomy and trabeculotomy. Sautter favours a more precise diagnosis than chronic open-angle glaucoma, as this is the collective label of dysgenetic, senile, and other changes in the angle. Aulhorn describes the subtle technique of profile perimetry, which allows the early recognition of small spot-like paracentral scotomata; she admits that this test for early glaucoma requires much time and patience. Draeger discusses the principles of tonometry with special reference to his hand applanation tonometer. Leydhecker deals with the drug treatment of glaucoma, and suggests treating the ischaemia of the optic nerve by Ronicol. It appears doubtful whether a drug which dilates the peripheral blood vessels may not produce an undesirable fall in the ophthalmic blood pressure. Witmer discusses the indications and techniques of operations for glaucoma.

This small book is stimulating and imparts much useful information.

Corneal Contact Lenses. Edited by L. J. GIRARD. 2nd ed., 1970. Pp. 348, 373 figs (91 in colour), bibl. Mosby, St. Louis; Kimpton, London (£10.35).

This is the second edition of the popular textbook on corneal lens fitting, which encouraged so many ophthalmologists in the United States to fit contact lenses.

The first edition described a method based upon corneal topography using a modified keratometer. This edition includes a chapter on trial lens fitting, which is possibly the most popular method in Britain. There are additional contributions by a non-medical practitioner.

It must be admitted that technology and the basic sciences are becoming of increasing importance in this specialty. The book has gained by remaining concise and avoiding a discursive approach, and now has some very well-produced slit-lamp colour photographs to illustrate fittings. It can be recommended to the student as a text that explains the principles of chairside fitting and the various techniques used in Mr. Soper's laboratory for the manufacture and modification of lenses.

Oculoplastic Surgery. By BYRON SMITH and T. D. CHERUBINI. 1970. Pp. 157, 55 figs. Mosby, St. Louis; Kimpton, London. (£8.30)

This book bears the evidence of having been written by two very experienced oculoplastic surgeons. It is a compendium and makes no claims of being encyclopaedic, but nevertheless describes with the help of clear illustrations so many principles and so many individual techniques used in plastic surgery around the eye that all surgeons will gain from reading it.

The views expressed are often somewhat personal, but when given by such experienced authors they have a claim to authority. It is refreshing to read of the advances made in even the simplest procedures upon the eyelid from the classical techniques described in the textbooks which have resulted from modern microsurgical techniques.

Eye Injuries. By E. ZAGORA. 1970. Pp. 601, 300 figs, 1 col. pl., bibl. Thomas, Springfield, Ill. (£30.75)

It is difficult to know for whom this work is intended. The preface is addressed to 'all who are responsible for therapy of such conditions'. However, if these include experienced eye surgeons, it was hardly necessary to illustrate such conditions as heterochromia (Fig. 2), hyphaema (Fig. 18), or hypopyon (Fig. 22). Surgeons in training might be misled by the prominence of photographs of a keratoprosthesis in the treatment of bullous keratopathy, and by the mention of the section of the greater superficial petrosal nerve in the treatment of this condition. Surely no eye surgeon needs to be shown a photograph of a man wearing goggles whilst using a hammer and chisel (Fig. 46).

Nevertheless, the book covers a wide field albeit in a highly personal manner, and is clearly the work of a widely experienced and enthusiastic surgeon. It would be of most use perhaps to an eye surgeon working single-handed in a busy industrial city.

Encyclopédie médico-chirurgicale. 25th Recueil: Ophtalmologie

The 29th *Cahier spécialisé* has now been published to bring up to date various aspects of ophthalmology in this interesting (if cumbersome!) encyclopaedia. The following subjects are included:

Oculomotor nerves—F. Hervouet, C. Lemasson, and H. Chevannes;
The trigeminal nerve—F. Hervouet, C. Lemasson, and H. Chevannes;
Physiology of the aqueous humour and ocular tension—P. Demailly;
Physiology of the ocular vessels—H. Hamard;
Retinal manifestations of toxicity—C. Haye;
Retinal conditions related to general disease and infections—C. Haye;
Simple malformations of the retina—H. Saraux;
Affections of the endocrine glands and nutritional disease—H. Hamard and L. Moreau;
Pathology of the ear in ophthalmology—M. Wayoff and P. Labaeye

As always, the contributors are specialists in their fields and these chapters are of considerable interest.

Print for the Visually Handicapped Reader. Papers and Proceedings of a Conference sponsored by The Library Association and the National Association for the Education of the Partially Sighted held on October 28, 1970 (Library Association Research Publication, No. 6). 1971. Pp. 64, refs. The Library Association, London. (75p)

Brit. J. Ophthal. (1971) 55, 718

Notes

Ophthalmological Society of the United Kingdom

91st Annual Congress, April, 1971

The 91st annual congress of the Ophthalmological Society of the United Kingdom was held at the Royal College of Physicians in London from April 21–23, 1971, under the Presidency of Prof. George Scott, C.B.E. This was the largest gathering that the Congress had known and among the 400 participants were the International Council of Ophthalmology, and many members of the European Ophthalmic Pathology Society and the Verhoeff Society from America.

The proceedings opened with an address of welcome from the President, which was followed by his Presidential Address on the past glories of Scottish ophthalmology. The Treacher Collins Prize was presented to Mr. R. F. Fisher for his essay on "The Eye and the Ageing Population".

The papers began with Mr. A. J. Bron and Mr. N. A. Brown introducing us to a two-dimensional world of superficial disorders of the corneae. Mr. W. M. Haining and Mr. H. M. McLean showed us the three-dimensional world revealed by the scanning electron microscope. Prof. Michael Hogan discussed the changes found in Reis-Bucklers corneal dystrophy. Mr. Montague Ruben then reviewed the role and problems of soft contact lenses and Mr. T. Stuart-Black Kelly stressed the value of contact lenses for the correction of unilateral aphakia. The main event of the afternoon was the Bowman Lecture given by Dr. Algernon Reese on "Expanding Lesions of the Orbit". It was an address of anticipated excellence from the doyen of the subject and was enhanced by the speaker's humility and candour.

The next day started with a Symposium on "The Dry Eye". Prof. Claes Dohlmann opened this with an account of the different types of dry eye and the role of ocular mucus. Mr. Peter Wright then dealt in detail with the day-to-day management of such cases. The systemic manifestations of Sjogren's syndrome were discussed by Dr. J. M. Gumpel and revealed features far more sinister than merely a dry eye. The role of localized corneal drying in relation to dellen and pterygia was discussed by Dr. Ian Mackie, who also laid great stress on alterations in blinking patterns and their association with Bell's phenomenon. Mr. J. Williamson and Mr. F. C. Rodger read papers in the discussion.

The afternoon programme began with a film about vertical gaze paresis from Mr. Bryan Ashworth, followed by three papers on the vitreous. Mr. Kennerly Banks discussed the relation of asteroid and scintillating bodies with diabetes mellitus. Mr. Frank Law described a unique case of vitreous anomaly, and Mr. J. D. Scott considered the role of vitreous movement in the formation of retinal tears. Dr. J. Penman introduced a medical note and discussed the management of four common types of facial pain. We were reminded by Dr. M. Jayson and Mr. D. Jones that rheumatoid arthritis is often associated with scleritis, particularly when systemic manifestations are present. The use of fluorescein angiography to study the iris was introduced by Mr. Hung Cheng, Mr. A. J. Bron, and Mr. D. Easty in a study of iris tumours, and Mr. Dermot Pierse closed the afternoon's proceedings by describing some refinements in the surgical removal of such lesions.

The last day was devoted to a discussion on the "Ischaemic Eye". Prof. W. R. Keatinge reminded us of the role of critical closing pressure and also introduced us to recent work on the activation of the smooth muscle within the vessel wall. Dr. David Knox presented a review of ischaemic ocular disease, stressing the importance of a general examination of the patient and the investigations necessary to uncover the cause. The choroidal circulation was described by Dr. S. Hayreh and the effect of acute and chronic occlusion of the large posterior ciliary arteries was presented. Prof. Paul Henkind introduced a general discussion on ischaemia of the posterior segment. Mr. K. Rubinstein considered the role of focal retinal ischaemia and the part which it played in producing retinopathy. Finally, Mr. M. Sanders discussed the clinical features of ischaemic optic neuropathy and dealt with the causes and treatment of this condition. Eleven other speakers took part in the discussion ranging from basic studies of the circulation to photocoagulation treatment of ischaemic retinopathy. The interest in this topic could be gauged by the fact that there were sufficient papers to fill the whole day and sufficient ophthalmologists to fill the seats until the end.

Ophthalmological Society of the United Kingdom

92nd Annual Congress, April, 1972

Preliminary Notice

The 92nd Annual Congress of the Ophthalmological Society will be held in the David Hume Tower, George Square, Edinburgh, on April 11 to 13, 1972.

The subject for discussion will be "Diabetic Retinopathy". Members who wish to take part are asked to intimate their intention before the opening of the Congress. The time allotted to such participators is 10 minutes each.

A symposium on "Pigmentary Retinopathy" will also be held.

Members are invited to submit papers, of either 10 or 20 minutes' duration, and these will be combined in a session relating to medical or surgical topics. Films of surgical procedures would be particularly welcome as contributions. For further information write to Mr. M. D. Sanders, Ophthalmological Society of the United Kingdom, Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London, WC2A 3PN.

European Society of Ophthalmology

II Symposium on the Lacrimal System, April, 1972

The second international symposium on the lacrimal system will be held on April 22 and 23, 1972, in association with the IVth Congress of the European Society of Ophthalmology to be held on April 17–21, 1972, in Budapest, Hungary.

Guest lecturers will include: F. Antoni, (*Hungary*); Milan Blagojevic, (*Yugoslavia*); Josef Bock (*Austria*); John Charamis, (*Greece*); A. Dubois-Poulsen, (*France*); Lester Jones, (*U.S.A.*); Benjamin Milder, (*U.S.A.*); John Clarke Mustardé, (*Scotland*); A. Neetens, (*Belgium*); M. Radnót, (*Hungary*); Salme Vannas, (*Finland*); Everett R. Veirs, (*U.S.A.*); Bernardo A. Weil, (*Argentina*), and A. Werb, (*England*).

Further information may be obtained from Everett R. Veirs, M.D., Chairman, Second International Symposium, Scott and White Clinic, Temple, Texas 76501, U.S.A. and from the Secretariat of the IVth Congress of the European Society of Ophthalmology, c/o Ist Eye Clinic University Medical School, VIII. Illes u. 15, Budapest, Hungary. The registration fee for the Second International Symposium is £10.00.

Royal College of Surgeons of England

Edridge-Green Lecture, 1971

The Edridge-Green Lecture on "Functional organization of the vertebrate retina" will be delivered by John. E. Dowling, Professor of Biology at Harvard University, on Thursday, November 18, 1971, at 5 p.m. at the Royal College of Surgeons, Lincoln's Inn Fields, London, WC2A 3PN.

No tickets are required.

Barraquer Medal, 1971

The 'Ignacio Barraquer y Barraquer' Silver Medal was presented to Dr. Jorge Vasco Posada of Antioquia, Colombia, on July 9, 1971, at the Barraquer Institute, Bogotá, for his work on the modification of the circulation of the posterior segment of the eye.

Concilium Ophthalmologicum Universale

Annual Meeting, 1971

The annual meeting of the International Council and of the International Committee of Ophthalmology was held in London on April 20, 1971.

The subjects chosen for the next International Congress, to be held in Paris in 1974, were Diabetic Retinopathy and Metabolic Disorders of Childhood.

Two new committees have been added to the existing sub-committees on standardization of tonometers and dynamometers, contact lenses, information as applied to ophthalmology, nomenclature of ocular diseases, and automotive safety:

1. To standardize the testing of colour vision.
2. To quantify compensation after ocular trauma.

Obituary

Edward Beric Alabaster, 1893—1971

Mr. E. B. Alabaster, who died on July 13, 1971, at the age of 78, joined the staff of the Birmingham Children's Hospital in 1922 as consultant ophthalmologist, succeeding Martin Young, and he served the hospital until 1946.

He qualified in 1916 and at once volunteered and joined the R.A.M.C., attaining the rank of captain and seeing service in Serbia and Salonika in the first world war. On his return he decided to specialize in ophthalmology and took the Diploma at Oxford in 1921. He was appointed surgeon to the Birmingham Eye Hospital in 1922.

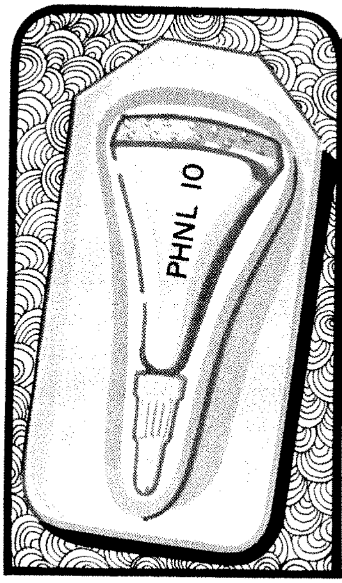
As consultant to the Children's Hospital he became intensely interested in the treatment of squint and initiated the first hospital orthoptic department in Britain. Under his guidance and with Miss D. Jones as head teacher, the orthoptic training school earned a nation-wide reputation. He also devised his own original squint operation using a gold bar splint. He became an authority on this subject, which he took for the Mary Louisa Prentice Montgomery Lecture which he was invited to give in Dublin in 1937. He was also a founder member of the British Orthoptic Board and served for many years on its examining panel.

He excelled as a surgeon and was the first in Birmingham to adopt the intracapsular method of cataract removal: his work was a revelation of delicacy and precision, and he was ever enthusiastic in the pursuit of new ideas and surgical techniques. He was elected F.R.C.S.Eng. in 1948. He was a prominent member of the Midland Ophthalmological Society, of which he was President from 1939 to 1943, and a regular attender at the Oxford Ophthalmological Congress.

Although ill-health forced him to relinquish his appointment at the Children's Hospital in 1946, he continued his service at the Eye Hospital until 1958, having served there for 36 years. Even after retirement he continued in consultation and in industrial clinics.

Outside his work, Alabaster was a keen golfer and his swing was as perfect as his cataract sections. After his round he often enjoyed a game of darts. Unfortunately ill-health in his later years prevented his enjoyment of his leisure time. He suffered a leg amputation when over 70, but continued his work, in spite of this handicap, until a very short time before his death after a second operation.

He was at all times a delightful companion and colleague and his death, which will be keenly felt, is a loss to ophthalmology in the Midlands. Our sympathy is extended to his widow and his family.



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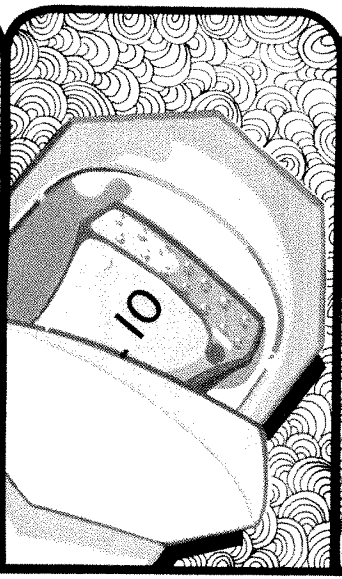

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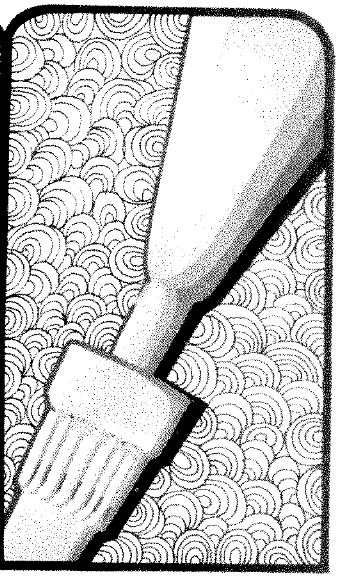

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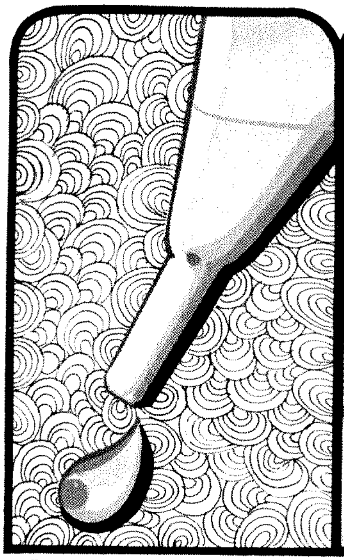

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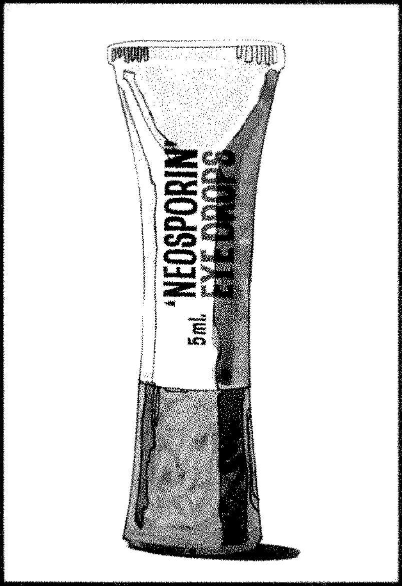

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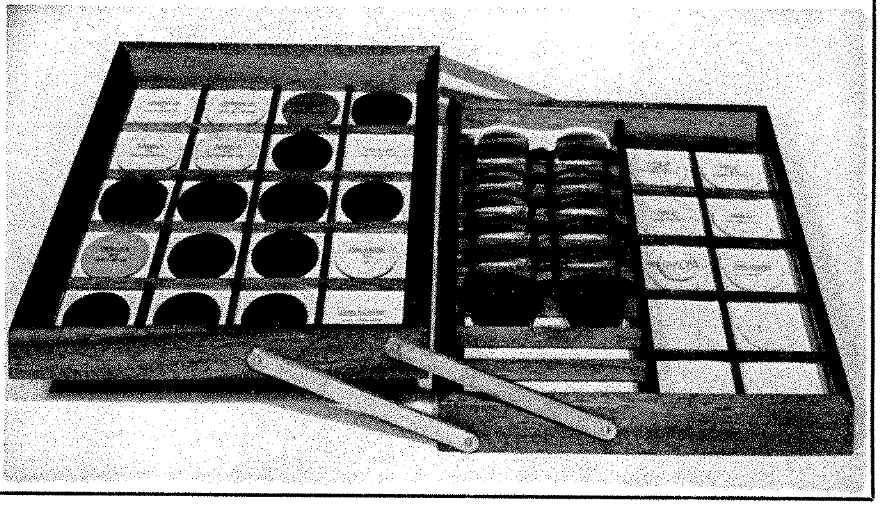

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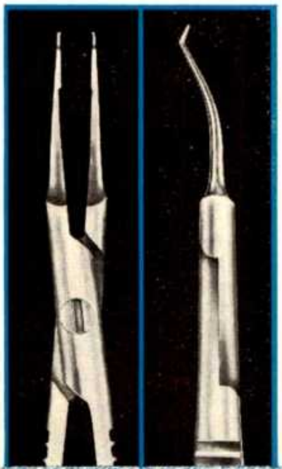

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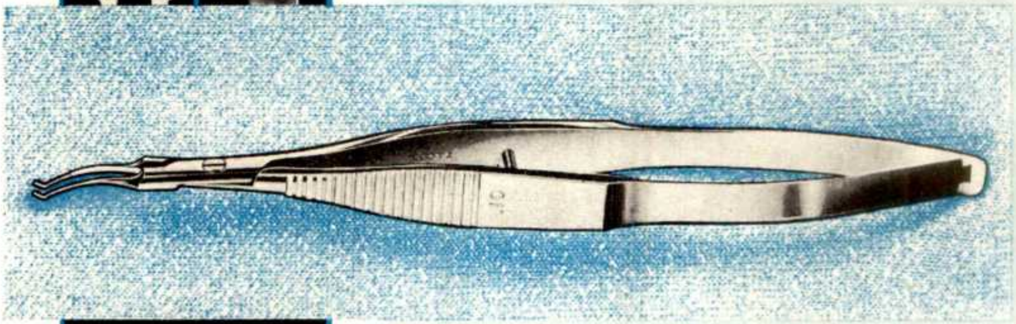

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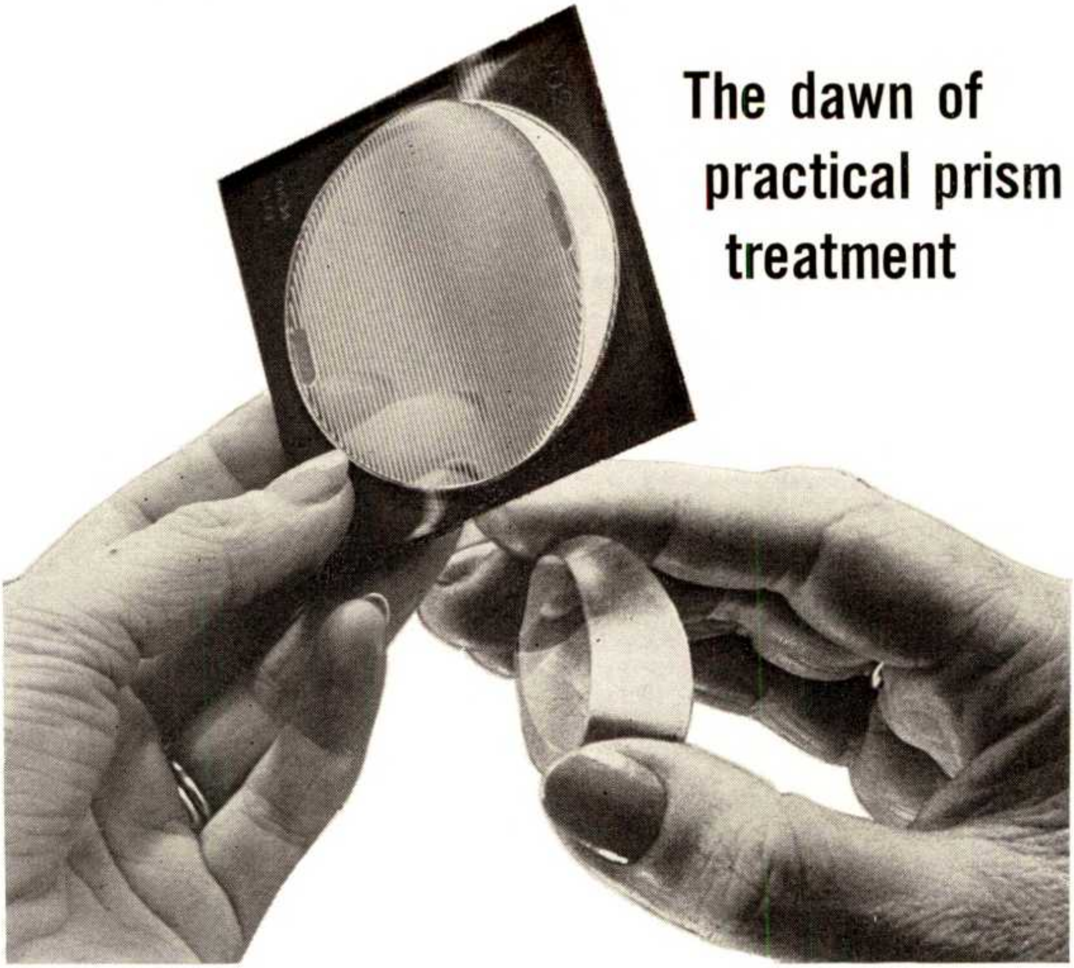

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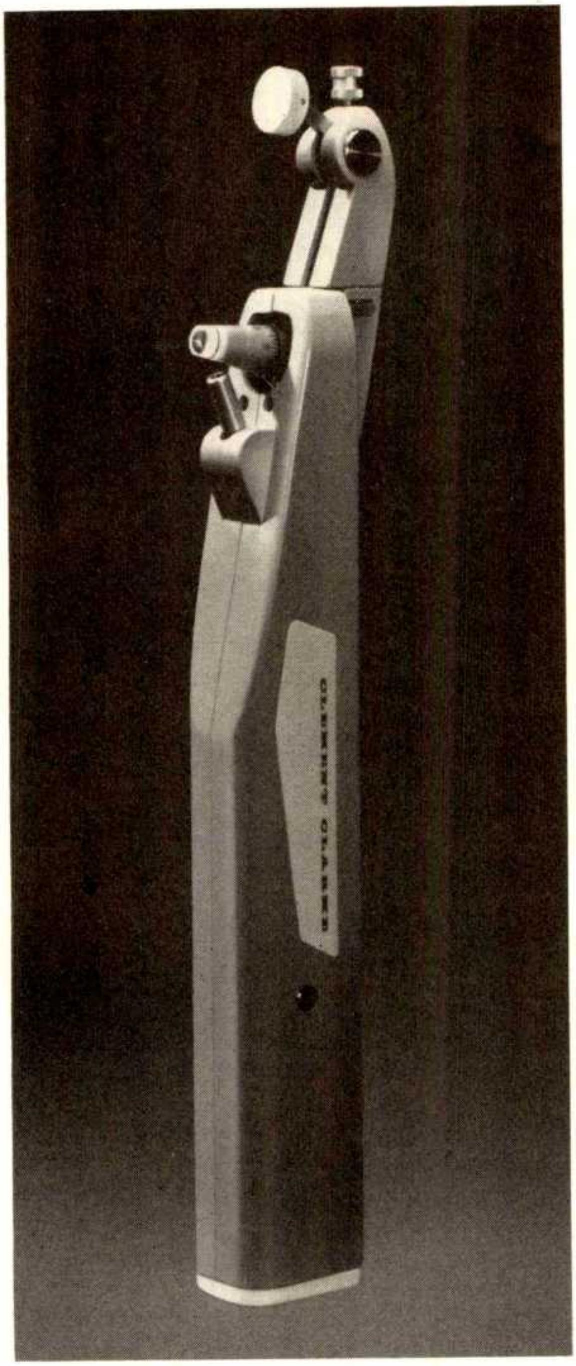

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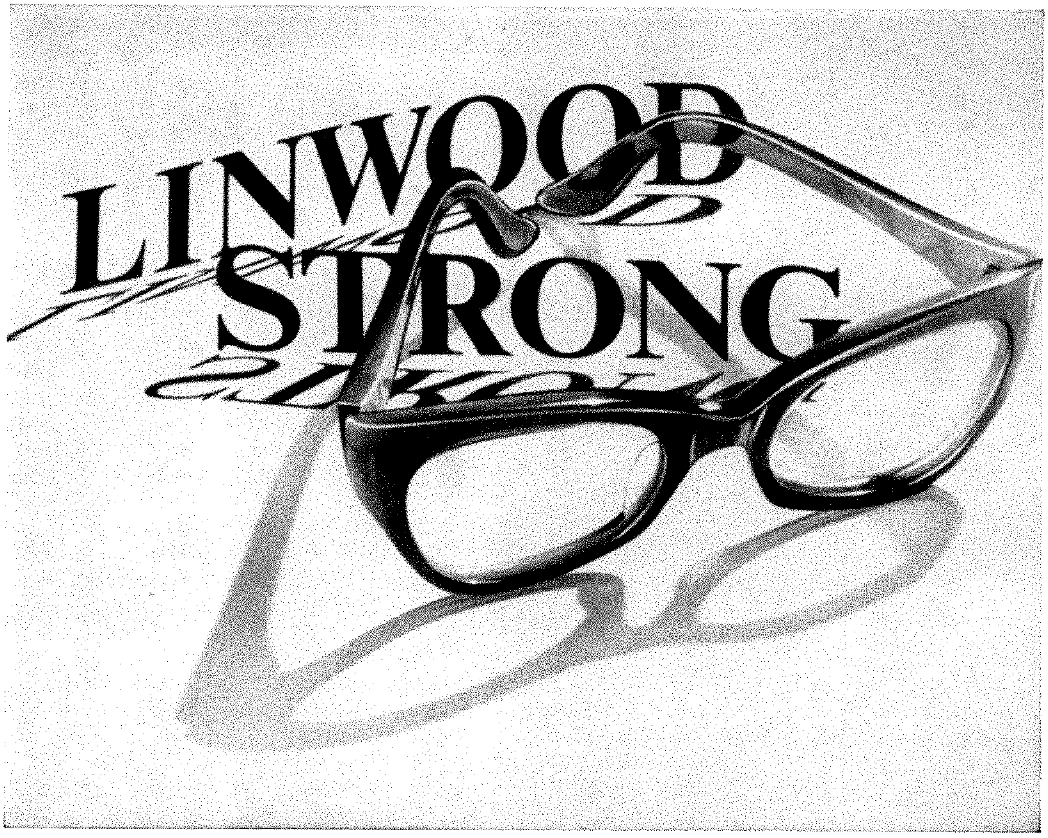

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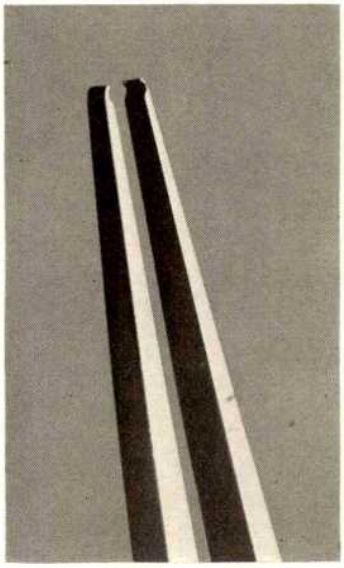

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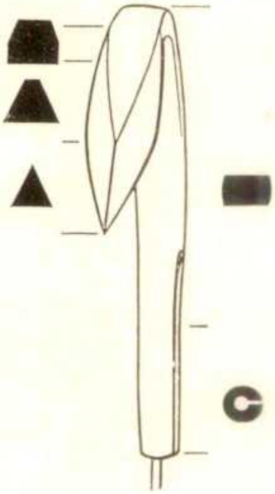

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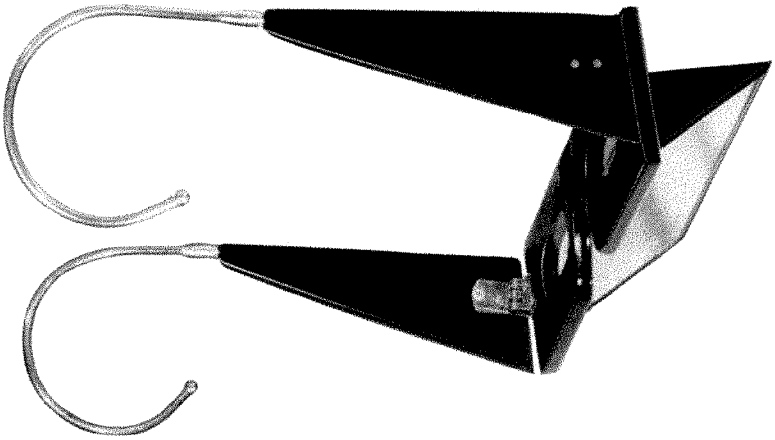

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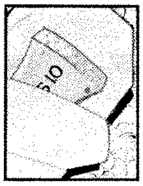

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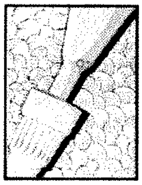

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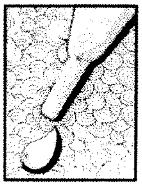

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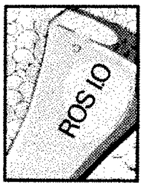

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Communications

Benign retinal vasculitis

Clinical and fluorescein angiographic study

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Central retinal vein occlusion occurs predominantly in the older age groups, and an increased incidence has been reported in association with systemic vascular disease (Paton, Rubinstein, and Smith, 1964), chronic simple glaucoma (Smith, 1955), high viscosity syndromes (Rowlands and Vaizey, 1938), and malignant disease (Ellis, Hamer, Hunt, Lever, Lever, Peart, and Walker, 1964). Central retinal vein thrombosis under the age of 40 years is infrequent (Vannas and Raitta, 1966), and both clinical (Lyle and Wybar, 1961) and pathological studies (Ballantyne and Michaelson, 1947) have suggested an inflammatory aetiology. The appearances in both groups are similar, but the visual loss and retinal changes are less severe in younger patients.

The first description (Lyle and Wybar, 1961), comprised six patients whose ages ranged from 14 to 49 years, who had minimal visual symptoms in spite of a florid retinopathy. The process was unilateral in five cases, and after resolution of the retinopathy mild sheathing of the veins and increased vascularity at the disc was seen in three cases. The sixth patient had cells in the anterior chamber in both eyes with a central vein occlusion on one side and a peripheral haemorrhagic retinopathy on the other. Lyle and Wybar postulated that the condition was mainly inflammatory, since the peripheral changes were similar to those of Eales's disease, and suggested the term retinal vasculitis. A further report of five cases (Lonn and Hoyt, 1966) substantiated the benign unilateral course of the condition and stressed the absence of inflammatory signs. Cogan (1969) divided his series into three groups according to the degree of severity and contributed both pathological and aetiological evidence on several cases. This paper presents a clinical and fluorescein angiographic study of nine cases of the syndrome of unilateral central retinal vasculitis occurring in patients under the age of 40 years. Patients with peripheral involvement and vitreous haemorrhages (Eales's disease) were excluded.

Case reports

CASE 1, A 21-YEAR-OLD WOMAN

This patient complained in February, 1967, of black spots in front of the right eye and blurring of vision for 3 days. She gave a history of intermittent frontal headaches for 9 months and was admitted to the National Hospital with a diagnosis of unilateral disc oedema.

Examination

The visual acuity was 6/24 in the right eye, and 6/6 in the left. The ocular media were clear and the left fundus normal. The right fundus had disc oedema with grossly dilated veins and scattered

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retinal haemorrhages extending to the equator. Perimetry revealed enlargement of the blind spot and a small central scotoma.

X ray examination of the skull and optic foramina was normal. The blood count and erythrocyte sedimentation rate were normal, and serological tests for syphilis gave negative results.

Fluorescein angiography 4 days after the onset of symptoms showed normal arterial filling but some delay in venous filling. Residual studies showed leakage from the region of the disc and in relation to the larger retinal veins.

Diagnosis

Retinal vasculitis.

Subsequent course

The patient was treated with 40 mg. prednisolone daily and this was reduced over a 2-month period without significant improvement. The disc oedema and retinal haemorrhages resolved over the next 18 months, so that when she was seen in November, 1969, the visual acuity was 6/5 and the fundus appeared to be normal apart from minimal sheathing of the larger retinal veins. Spontaneous venous pulsation was present in both eyes.

Fluorescein angiography showed a normal dye transit with no leakage in the residual photographs.

Summary

A healthy young woman had mild visual loss from retinal vasculitis. Complete resolution occurred over an 18 month period leaving residua of sheathing of the retinal veins.

CASE 2, A 35-YEAR-OLD MAN

This patient complained of black spots and blurring of vision in the right eye in November, 1969. These symptoms lasted for 3 days and then subsided, but 3 days later the right vision again became blurred. A diagnosis of unilateral disc oedema was made and the patient was admitted to the National Hospital for investigation in January, 1968. He had no significant past history.

Examination

The visual acuity was 6/9 in the right eye and 6/6 in the left. The ocular media were clear and the left fundus was normal. In the right eye there was disc oedema with dilatation of the veins and numerous haemorrhages and cotton wool spots. Perimetry showed enlargement of the blind spot.

X ray examination of the skull and optic foramina was normal. Serological tests for syphilis gave negative results.

Fluorescein angiography 2 months after the onset of symptoms showed normal dye transit and residual studies demonstrated leakage around the disc and larger veins.

Diagnosis

Retinal vasculitis.

Subsequent course

No treatment was given. The visual acuity returned to 6/6 within 6 months and this was associated with complete resolution of the abnormal fundus appearances. Repeat fluorescein studies showed normal transit without any leakage in the residual studies.

Summary

A healthy young man developed retinal vasculitis with mild visual loss and complete resolution occurred over a 6-month period.

CASE 3 A 31-YEAR-OLD MAN

This patient complained of blurring of vision and blank areas in his visual field for 3 days when first seen in October, 1969. There were no relevant past illnesses.

Examination

The visual acuity was 6/9 in the right eye and 6/6 in the left. The ocular media were clear and the left fundus normal. The right fundus showed disc oedema, the retinal veins were grossly engorged, and there were cotton wool spots and numerous haemorrhages. The retinal periphery was normal. Spontaneous venous pulsation was present in the left eye but not in the right.

Perimetry showed enlargement of the blind spot and two small paracentral scotomas.

X rays of the skull and optic foramina were normal. The erythrocyte sedimentation rate and blood count were normal. Serological tests for syphilis gave negative results.

Ophthalmodynamometric studies showed arterial pressures of 110/65 in the right eye and 110/60 in the left.

Fluorescein angiography 5 days after the onset of symptoms showed a rapid arterial transit with slow filling of the veins. Residual studies showed massive leakage of dye in relation to the disc and larger veins.

Diagnosis

Retinal vasculitis.

Subsequent course

The patient was treated with 30 mg. Prednisolone daily. This therapy was stopped after 6 weeks as no significant improvement had occurred. The abnormal fundus appearances resolved over a 2-month period, leaving mild pigmentary abnormalities in the macular region. The visual acuity improved to 6/6 though the patient complained of micropsia. Spontaneous venous pulsation was now present in both eyes. The fluorescein angiogram was repeated and a normal transit was recorded with minimal leakage in the region of the disc.

Summary

A healthy young man developed retinal vasculitis with mild visual impairment. Complete resolution occurred within 2 months, though the symptoms of micropsia persisted and some pigmentary changes were noted at the macula.

CASE 4 A 31-YEAR-OLD MAN

This patient woke up one morning with blurring of vision and a shimmering sensation in the temporal half of the left visual field in December, 1969. He also complained of mild frontal headaches.

Examination

10 days later the visual acuity was 6/6 in each eye. The ocular media were clear and the right fundus normal. The left fundus showed disc oedema, dilated tortuous veins, cotton wool spots, and haemorrhages extending to the equator. Ophthalmodynamometry showed arterial pressures of 105/60 and 110/65 in the right and left eyes respectively. Venous pulsation was present spontaneously in the left eye and was elicited at a pressure of 50 mm.Hg in the right. Perimetry demonstrated enlargement of the blind spot.

X ray examination of the skull and optic foramina was normal. No haematological abnormality was detected. Serological tests for syphilis gave negative results.

Fluorescein studies 14 days after the onset of symptoms showed rapid passage of dye through the retinal vessels but with profuse leakage in the later stages from the major veins and in relation to the disc (Fig. 1*a*, overleaf).

Diagnosis

Retinal vasculitis.

Subsequent course

3 weeks after the first onset of symptoms the vision in the left eye deteriorated to 6/36. The disc swelling had increased, the veins were more dilated and tortuous, and the number of haemorrhages and exudates had increased. Fluorescein studies showed a slow transit, dilatation of the arterioles, venules, and capillaries, and marked leakage of dye in all areas.

The patient was admitted for investigation in March, 1970, when the visual acuity remained at 6/36. The gross retinal changes had partly resolved and fluorescein studies showed a normal retinal transit. The capillaries were dilated with microaneurysm formation and extensive leakage of dye (Fig. 1*b*). The macular region showed the appearances of cystoid maculopathy.

Further resolution had occurred when he was seen in May, 1970, and the vision had improved to 6/6, though he still complained of micropsia. There were fine scattered retinal haemorrhages but no exudates. Fluorescein studies showed a normal flow pattern; the paramacular capillaries were dilated but no leakage was observed in the late photographs. Complete resolution had occurred when this patient was last examined in February, 1971.

Summary

A healthy 31-year-old man developed sudden mild visual impairment and retinal vasculitis was diagnosed. Severe visual impairment developed after 3 weeks and was associated with increased capillary permeability in the macular region. Spontaneous resolution occurred over a 6-month-period.

CASE 5 A 21-YEAR-OLD MAN

This patient first became aware of bright spots in the temporal field of the right eye in December, 1968, and was referred for fluorescein studies by Mr. Geoffrey Davies of King's College Hospital in February, 1969. He had suffered no relevant previous illnesses.

Examination

The visual acuity was 6/9 in the right eye and 6/5 in the left. The ocular media were clear and the left fundus normal. The right fundus had disc oedema, the retinal veins were grossly dilated, and there were numerous cotton wool spots and haemorrhages extending to the periphery (Fig. 2*a*, overleaf). The retinal periphery appeared normal. Spontaneous venous pulsation was present in the left eye but absent in the right.

Perimetry showed enlargement of the blind spot.

X ray examination of the skull and optic foramina was normal. No haematological abnormality was detected. Serological tests for syphilis gave negative results.

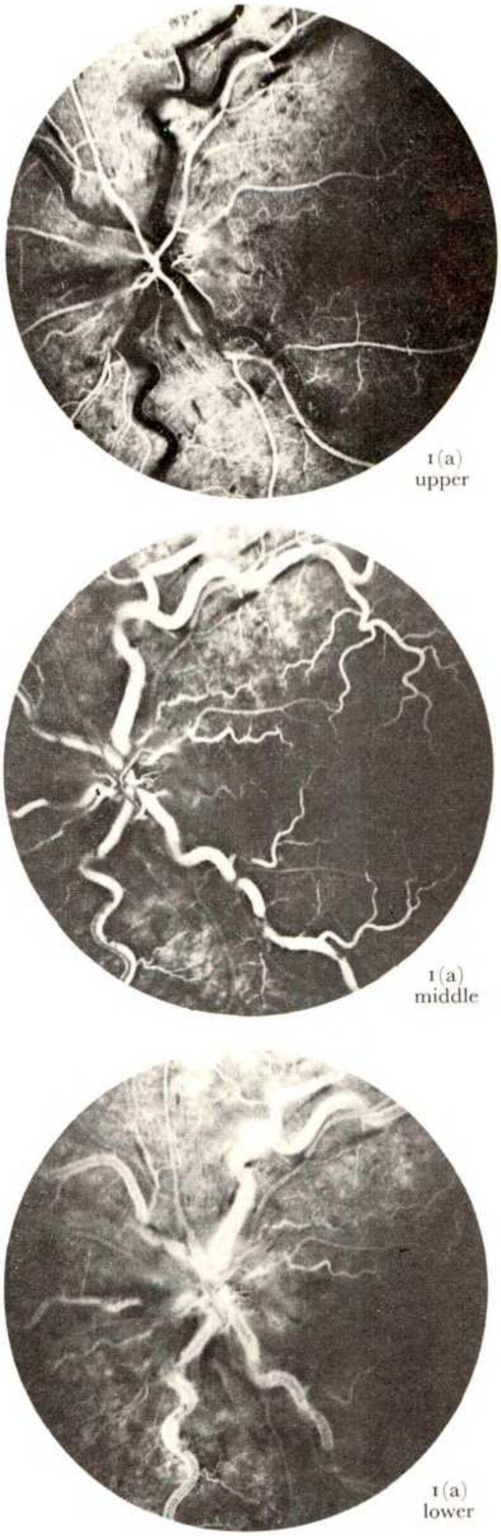
Fluorescein angiography 2 months after the onset of symptoms revealed a relatively normal flow through the arteries and veins, but leakage of dye was seen in the residual studies in the region of the disc and in relation to the larger veins.

Diagnosis

Retinal vasculitis.

Subsequent courase

The patient was seen again in January, 1970, when the vision in the right eye had improved to 6/6. The haemorrhagic retinopathy had resolved, though the veins, which were of normal calibre, showed mild sheathing. Numerous shunt vessels were nowapparent in relation to the disc (Fig. 2*b*, overleaf). Spontaneous venous pulsation was present in both eyes.

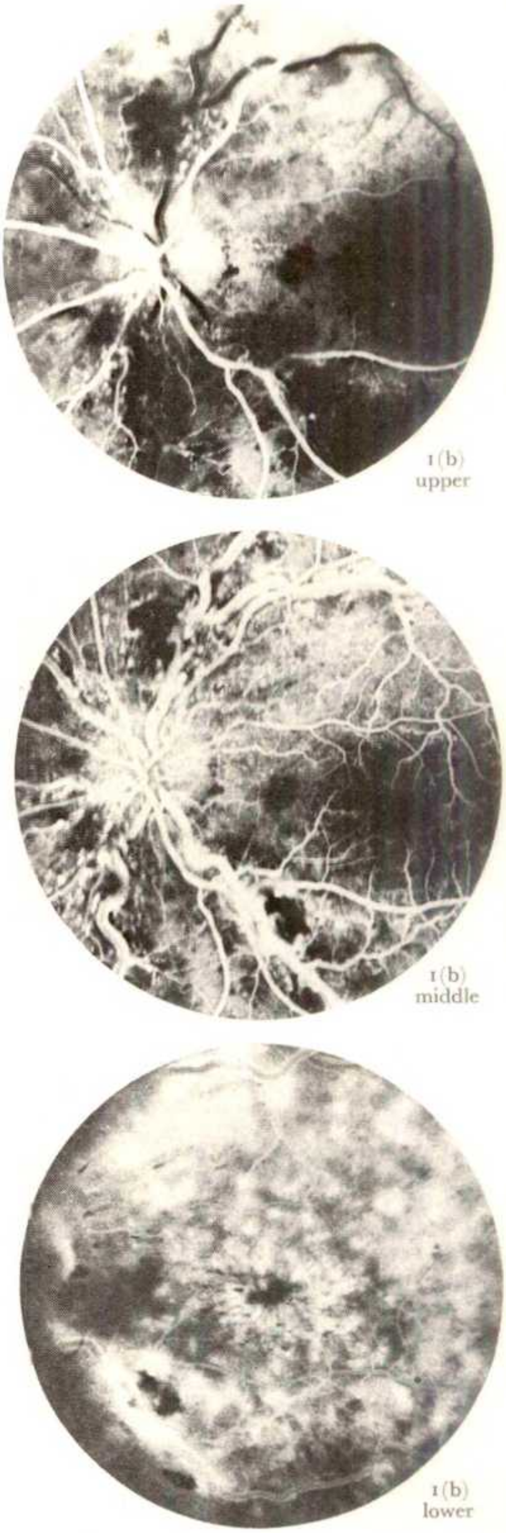


1(a) upper

1(a) middle

1(a) lower

FIG. 1(*a*) *Case* 4. *Fluorescein angiograms in the arterio-venous* (*upper*), *venous* (*middle*), *and residual phases* (*lower*), *to show the stage of venous decompensation. The veins are grossly dilated and there is perivenous leakage of dye. Capillary flow is intact and the visual acuity at this stage was* 6/6



1(b) upper

1(b) middle

1(b) lower

FIG. 1(*b*) *Case* 4, 3 *months later. The fluorescein angiograms are comparable and show the stage of capillary decompensation. The veins remain dilated but gross capillary dilatation is seen with microaneurysm formation. In the residual phase extensive capillary leakage has produced the appearances of cystoid maculopathy. Visual acuity was* 6/36

Fluorescein angiography showed rapid transit of dye through the retinal vessels and no leakage of dye in the residual photographs. The shunt vessels in the region of the disc filled in the venous phase.

Summary

A young man developed retinal vasculitis, and complete resolution occurred within 12 months with shunt vessels at the optic disc.

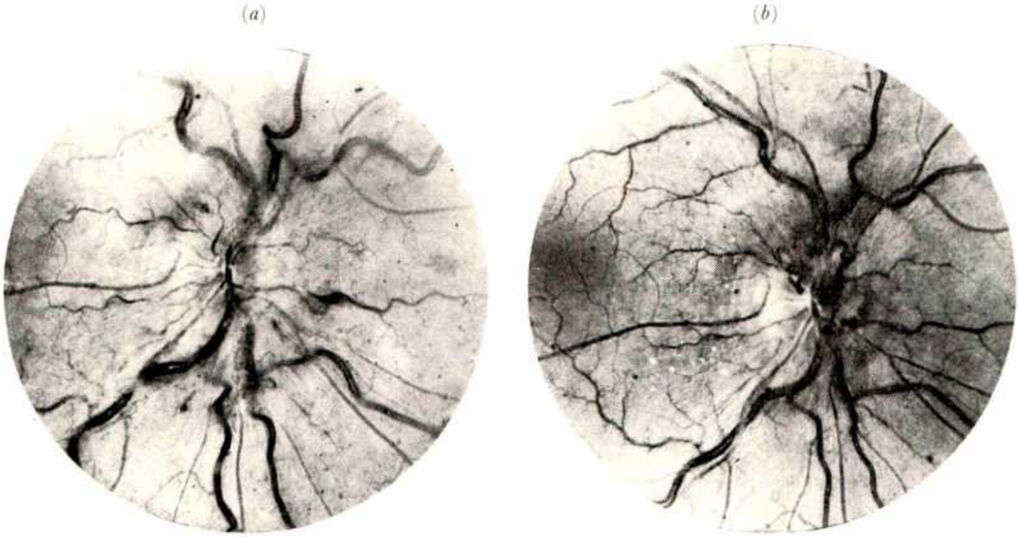


FIG. 2 *Case 5. Copies of colour photographs to show the disc appearances in the active stage (a) and the development of shunt vessels at the optic disc (b) after resolution*

CASE 6 A 20-YEAR-OLD MAN

This patient was seen in September, 1970, with a history of a shimmering sensation in front of the right eye and some blurring of vision. These symptoms were present on waking in the morning and cleared within 30 minutes. When he was seen by Mr. Davies of King's College Hospital the visual acuity was 6/6 in each eye. The anterior chambers were normal on both sides and the left fundus appeared normal. In the right eye there was marked disc oedema with gross dilatation of the retinal veins and haemorrhages extending to the equatorial region.

Perimetry showed slight enlargement of the blind spot.

X ray examination of the skull and optic foramina was normal. Routine haematological studies were normal. Serological tests for syphilis gave negative results.

Ophthalmodynamometry readings showed pressures of 120/65 in each eye. The venous pressure in the right eye was 60 mm.Hg whereas in the left eye there was spontaneous venous pulsation.

Diagnosis

Retinal vasculitis.

Subsequent course

In October, 1970, resolution of the retinopathy had occurred and fluorescein angiography showed mild residual leakage in relation to the disc.

Summary

A young man was found to have retinal vasculitis; there was complete resolution in 6 weeks without any treatment and there were no residual signs.

CASE 7 A 24-YEAR-OLD MAN

This patient was referred by Mr. J. N. Ormrod of Maidstone with a history of blurring of vision in the right eye in November, 1970; 2 weeks later the visual acuity in the right eye deteriorated to 6/9, and a week later to 6/18.

Examination

The visual acuity was 6/24 in the right eye and 6/5 in the left. Several discrete areas of blurring were noted with the Amsler chart and the visual fields showed enlargement of the blind spot and a relative central scotoma. The fundus showed marked disc swelling with gross dilatation of the veins, numerous cotton wool spots, and haemorrhages extending to the periphery. The left fundus was normal. Ophthalmodynamometry showed diastolic arterial pressures of 60 mm. Hg in each eye. The venous pressure was 10 mm. Hg in the left eye and 55 mm. Hg in the right.

X ray examination of the skull and optic foramina was normal. Serological tests for syphilis gave negative results. The only haematological abnormality was elevation of the alpha 2 globulin.

Fluorescein angiography showed normal arterial filling but with a slow transit of dye to the venous side and with some dilatation of the peripapillary capillary plexus in the lower half of the disc, and of the capillaries in the macular region. Residual photographs after 10 minutes showed marked leakage of dye into the retina, but particularly around the disc and along the larger veins.

Diagnosis

Retinal vasculitis.

Subsequent course

The patient was treated with 40 mg. prednisolone daily and later with ACTH.

As there was no improvement Diamox was also administered in an attempt to improve ocular perfusion.

Summary

A young man developed retinal vasculitis and the condition resolved after 2 months.

CASE 8 A 33-YEAR-OLD MAN

This patient complained in January, 1970, of sudden severe visual loss in the right eye on waking. He also gave a history of headaches for 6 months.

Examination

The visual acuity was counting fingers in the right eye and 6/6 in the left. The media were clear, The left fundus was normal. The right fundus showed gross disc oedema with peripapillary cotton wool spots, and the engorged veins were surrounded by haemorrhages extending to the periphery.

Ophthalmodynamometry showed diastolic readings of 88 in the right eye and 90 in the left eye and, whereas there was spontaneous venous pulsation in the left eye, the venous pressure in the right eye was 80 mm.Hg. The blind spot was enlarged and a central scotoma was present.

The blood pressure was 200/120 and an electrocardiogram showed evidence of mild left ventricular hypertrophy. Radiological and haematological investigations were otherwise normal. Serological tests for syphilis gave negative results.

Fluorescein angiography 8 days after the visual deterioration showed rapid filling of the arteries, though there was some degree of attenuation and variation in calibre of the vessels. The veins were dilated and filling was delayed. Residual studies showed marked leakage of fluorescein from the region of the disc and along the large veins.

Diagnosis

Retinal vasculitis.

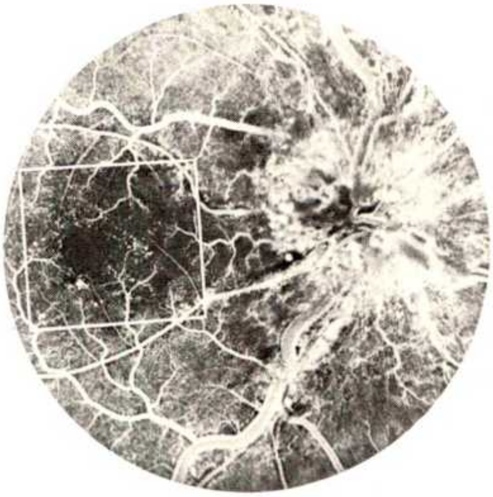
Subsequent course

Studies were initiated to assess the systemic hypertension.

When the patient was seen again 9 months later the visual acuity had improved to 6/12 though he still complained of micropsia. There was still marked disc oedema with dilated veins and oedema in the macular region. There was also early disc oedema in the left eye with a few retinal haemorrhages in the peripapillary region.

Fluorescein angiography was repeated and the arterial appearances were found to be unchanged. The capillary pattern in the posterior pole and perimacular region was abnormal. There were areas of capillary closure, and some capillaries were dilated to form preferential channels with microaneurysms (Fig. 3). Residual leakage of fluorescein was seen at the disc and along the major veins.

(3a)



(3b)

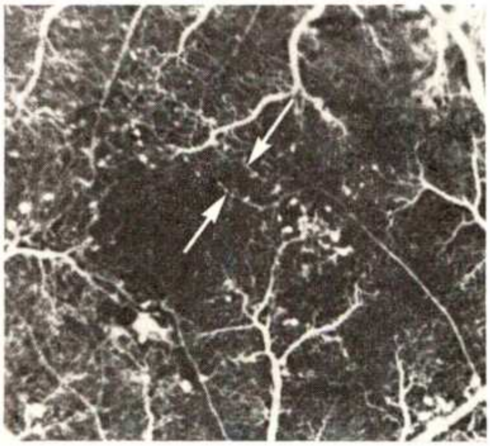


FIG. 3(*a*) *Case* 8. *Arterio-venous fluorescein angiogram* 8 *months after onset in this patient with hypertension. The arteries are attenuated, the capillaries show areas of closure with microaneurysm formation, and the veins are distended. Marked leakage of dye was visible in the residual photographs. The visual acuity was reduced to* 6/36.

FIG. 3(*b*) *Insert of Fig.* 3(*a*) *enlarged to show capillary dilatation with microaneurysm formation, areas of closure, and development of arterio venous-preferential channels (arrows).*

Summary

A young man presented sudden loss of vision in one eye and the clinical appearances of a retinal vasculitis. Systemic examination showed that he was suffering from malignant hypertension.

CASE 9 A 37-YEAR-OLD MAN

This patient referred by Mr. Peter Wright of King's College Hospital in January, 1971, with a week's history of sudden loss of temporal vision in the right eye. He complained of a dark shadow on the temporal side. There were no relevant previous illnesses though he had been kicked in the right eye some years previously.

Examination

The visual acuity was 6/9 in the right eye, and 6/6 in the left, with a small myopic correction. The blind spot on the right side was enlarged and objects were slightly dimmer on the temporal side.

Ophthalmodynamometry showed arterial pressures of 90/40 in each eye. The venous pressure was 40 mm.Hg in the right eye, whereas spontaneous venous pulsation was present in the left.

The left fundus was normal. The right disc was swollen, and the veins were grossly dilated with numerous haemorrhages and a few cotton wool spots in the posterior pole extending to the periphery.

X ray examination of the skull and optic foramina was normal. Haematological tests and serological tests for syphilis gave negative results.

Fluorescein angiograms showed normal arterial flow, with delayed venous filling and perivenous leakage in the late phases.

Diagnosis

Retinal vasculitis.

Subsequent course

The patient was seen again 6 weeks later, when the retinopathy had settled apart from a few resolving haemorrhages and small shunt vessels were visible at the optic disc. The visual acuity had improved to 6/5, Ishihara testing was normal, the visual field was normal, and venous pulsation was visible in the right eye.

Summary

A 37-year-old man experienced the sudden onset of retinal vasculitis. This resolved over a 6-week period and shunt vessels were visible at the optic disc.

Results

VISUAL SYMPTOMATOLOGY

Presenting visual complaints ranged from ill-defined blurring of vision to more specific complaints such as multiple small scotomata, black spots, and 'shimmering' sensations. These were often associated with good visual acuity and in one patient the symptoms were present on waking in the morning but subsided after 30 minutes. In three further patients the visual symptoms occurred suddenly. Severe visual loss, when present, was correlated with permeability defects in the capillaries in the macular region on fluorescein angiography. Micropsia was reported in three cases after resolution of the retinopathy.

OCULAR SIGNS

Ocular examination indicated more extensive involvement than the symptoms would suggest and consequently four cases were immediately referred to neurologists for further investigation of unilateral papilloedema. The similarity of the physical signs in our group, however, facilitated diagnosis, since all the patients had marked disc oedema, peripapillary cotton wool spots, and grossly dilated tortuous veins with perivenous haemorrhages extending to the periphery. Slit-lamp examination showed no activity in the anterior chamber in any case.

OPHTHALMODYNAMOMETRY

Readings were performed in six cases and the arterial pressures were equal in both eyes. Spontaneous venous pulsation was present in the non-affected eyes, but absent in the involved eyes, in all cases.

Measurements in five cases showed grossly elevated venous pressure to figures which were approaching the diastolic arterial pressure (Table I).

Table *Ophthalmodynamometry readings in five cases*

Case no.	*Vessels*	*Eye*	
		Normal	*Involved*
5	Arterial Venous	105/60 Spontaneous pulsation	110/60 50
6	Arterial Venous	120/65 Spontaneous pulsation	125/65 60
7	Arterial Venous	90/60 Spontaneous pulsation	90/65 55
8	Arterial Venous	Diastolic 88 Spontaneous pulsation	Diastolic 90 80
9	Arterial Venous	90/40 Spontaneous pulsation	90/40 38

COURSE

Complete resolution occurred in eight cases, and the duration before recovery ranged from 6 weeks to over a year. Residual signs included sheathing of the veins, macular pigmentary changes, and the development of shunt vessels around the disc in two cases. Resolution of the retinopathy was incomplete in one patient (Case 8) in whom a systemic disease was detected.

FLUORESCEIN RESULTS

Rapid fluorescein fundus photographs were performed, using the modified Zeiss camera, after the injection of 5 ml. 20 per cent fluorescein. Arterial filling was slow in the cases seen within the first few days of onset, but normal in all cases seen in the later stages. One case with systemic disease had irregularity of the arteries with impaired flow. Venous filling was delayed during the active phase, but in repeat studies, performed after resolution, the venous transit was normal. Abnormalities in the paramacular capillaries were noted in four patients whose visual acuity was diminished to 6/18 or less. The capillary changes consisted of dilatation, closure with microaneurysm formation, and the development of preferential shunt channels. These changes were associated with increased permeability to fluorescein. Residual photographs taken 10 minutes after injection showed a massive leakage of dye from the region of the disc and along the larger veins.

Discussion

AETIOLOGY OF CENTRAL RETINAL VASCULITIS

The appearances of retinal vasculitis and central retinal vein occlusion are similar, both clinically (Klien and Olwin, 1956) and on fluorescein angiography. Pathological studies of severely involved eyes with thrombotic glaucoma have shown evidence of arterial disease, primary venous disease (Klien and Olwin, 1956), and inflammatory disease (Ballantyne and Michaelson, 1937). However, no pathological studies have been made of the benign form of retinal vasculitis.

The evidence for an inflammatory aetiology is tenuous, as only one case in previous reports (Lyle and Wybar, 1968; Lonn and Hoyt 1966) and none in the present series had cells in the anterior chamber. Furthermore, it is well recognized that the finding of cells in the anterior chamber is frequent in ischaemic ocular disease (Knox, 1965; Sanders and Hoyt, 1970). Cellular cuffing of the retinal veins distal to the site of occlusion has recently been described (Kohner, Dollery, Shakib, Henkind, Paterson, de Oliveira, and Bulpitt, 1970) after experimental branch vein thrombosis. Similarly, inflammatory cell sheathing has been observed in Eales's disease (Ashton, 1962) and in inflammatory central retinal vein thrombosis (Klien, 1960). In these cases the cuffing consisted mainly of round cells, whereas in the experimental vein occlusions the cells were predominantly polymorphonuclear leucocytes. The relatively short duration of the occlusion in the experimental group before histology may be of significance. The finding of haematological abnormalities in Eales's disease (Ashton, 1962) and the similar retinal findings in sickle cell haemoglobin disease may indicate a non-inflammatory aetiology. Central retinal vasculitis, although it affects predominantly young adult males, has no other feature in common with Eales's disease. The condidion is unilateral, peripheral retinal vessels are not involved. vitreous haemorrhages are absent, and resolution without recurrence is the rule.

Experimentally, the site of central retinal vein occlusion determines the severity of the resulting retinopathy, being limited to venous dilatation when the occlusion is outside the nerve (Hayreh, 1965) but producing a gross haemorrhagic retinopathy when at or close to the nerve head (Fujino, Curtin, and Norton, 1969). Occlusion of the central retinal vein distal to the anastomoses with the choroidal and pial circulation extensively reduced retinal perfusion so that fluorescein studies revealed defective arterial transit, whereas occlusions proximal to the collaterals produced minimal changes. Thus the site of occlusion may be important in determining the pattern and prognosis in central retinal vein occlusion and central retinal vasculitis. An anatomical variation in the emergence of the central retinal vein from the optic nerve sheath has been postulated in relation to central retinal vein occlusions in adults (Harms, 1905), and this has not been excluded in the mechanism of vasculitis.

PATHOPHYSIOLOGY

Controversy exists as to the role of arterial insufficiency in retinal vein thrombosis. It has been thought to be important on clinical (Paton, Rubinstein, and Smith, 1964), pathological (Klien and Olwin, 1956), and experimental evidence (Hayreh, 1965). Ophthalmodynamometry (OD) recordings in a series of 73 cases with central retinal vein occlusion showed reduction of the systolic pressure in 30 per cent. (Smith, 1964).

Arterial OD recordings in our series showed normal pressures which were equal in each eye. The venous pressure was elevated in all cases with absent spontaneous pulsation. Measurement by ophthalmodynamometry, when performed, showed marked elevation in all cases to levels approaching the diastolic arterial pressures. *Thus it appears that the single important factor in this group is a reduction in the arterio-venous pressure gradient (perfusion pressure) produced solely by elevation of the venous pressure.*

The absence of arterial disease with maintenance of a normal arterial pressure may be the main reason for the good prognosis in this group. This is supported by the fact that the one patient in this group with arterial disease due to malignant hypertension (Case 8) had severe visual loss with gross capillary decompensation. Similarly, in the severe cases described by Cogan (1969), there was a high association with systemic disease. The poorer prognosis in older patients is probably due to their impaired ability to form collateral channels and to the higher incidence of arterial disease. 86 per cent. were found to have associated arterial system disease (Paton and others, 1964). However, some patients in the older age group with no signs of arterial disease may have a good prognosis and may also develop collateral channels.

Fluorescein studies indicate that there are two main patterns of vascular decompensation:

(1) In the first group the most significant factor is venous decompensation. The veins which are dilated show perivenous fluorescence in the late photographs, and this is most marked in the concavity of the vein. The capillaries, though they may be somewhat dilated, are not permeable to fluorescein and there are no microaneurysms. The clinical appearance at this stage shows a moderate retinopathy with haemorrhages and cotton wool spots but with minimal retinal oedema. The visual acuity at this stage is usually only slightly reduced.

(2) The second more severe stage is that of capillary decompensation. This is characterized by dilated capillaries often with microaneurysms and extensive leakage of dye. The clinical appearances show an extensive retinopathy with retinal oedema and the visual acuity is impaired. The macular region may give the appearances of a cystic maculopathy and this has been described with central retinal vein occlusion by Gass (1968).

The capillary closure may be due in part to elevation of tissue pressure, either because of ischaemic cellular oedema of the retinal elements or because of failure of tissue fluid to be absorbed in the venous capillaries, since intraluminal pressure exceeds the plasma protein osmotic pressure (Kohner and others, 1970). The propensity of the retina for swelling and the sensitivity to ischaemia is particularly high in the macular region (Wise and Wangvivat, 1966).

Shunt vessels at the optic disc have been described in retinal vasculitis (Lyle and Wybar, 1961; Lonn and Hoyt, 1966) and in retinal vein occlusion (Vannas and Raitta, 1966). They have been recorded in chronic disc oedema (Sanders, 1969) and seen in papilloedema (personal observation). Pathological studies in central retinal vein occlusion (Klein, 1960) and in papilloedema (Paton and Holmes, 1911) have confirmed the existence of large retino-choroidal anastomoses. Development of the preferential channels was noted in two of our patients in whom a satisfactory visual result was obtained. Development of these channels would seem possible only when the occlusive process occurs within the proximal portion of the vein as it lies in the optic nerve.

CONCLUSION

A series of patients with a benign form of central vasculitis has been described, in only one of whom was an associated systemic disease detected. All were under the age of 40 years so that their vascular systems and potential for developing collateral channels was considered normal.

The symptomatology was often characteristic with a variety of complaints and in three cases the sudden onset favoured a vascular occlusive phenomenon. The visual acuity was only slightly impaired, though the retinopathy was striking. Ophthalmodynamometry readings showed normal arterial pressures with grossly elevated venous pressures. Fluorescein studies demonstrated a normal arterial filling, a slow transit of dye, and marked residual leakage in relation to the disc and larger veins. Visual loss, when it occurred, was associated with capillary decompensation and leakage of dye occurring particularly in the macular region. Resolution occurred within a period of several months with a return to normal visual acuity, but often with persistent micropsia, and in some cases fundus changes consisting of venous sheathing and pigmentary changes at the macula.

It is concluded that the main haemodynamic effect is a reduction in perfusion pressure which is due solely to the elevated venous pressure. The condition is analogous and possibly identical to retinal vein occlusion in the older age groups, though in the latter the prognosis is poor because of the associated arterial disease and relative inability to develop proficient collateral circulation. The site of occlusion is an important factor.

The aetiology remains obscure, and probably diverse, for many different mechanisms may produce venous obstruction at any site. The systemic administration of steroids does not appear to be specifically efficacious in treatment, and methods at present employed include the systemic administration of Diamox in an attempt to improve ocular perfusion.

This series has not included those cases with vitreous haemorrhages, peripheral neovascularization, and absolute glaucoma, which represent a separate group.

Summary

A series of patients under the age of 40 years with benign central vasculitis has been studied by ophthalmodynamometry and fluorescein angiography. The main haemodynamic abnormality is a reduction in the perfusion pressure which is due to elevated venous pressure. Fluorescein studies show two phases of involvement depending on whether the veins alone or both veins and capillaries are decompensated. The visual outcome is favourable in all cases unless associated systemic disease is present.

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Preservation of sodium bicarbonate eye lotion BPC against contamination with *Pseudomonas aeruginosa*

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BPC (1968) eye lotions are sterile aqueous solutions which do not contain an antibacterial preservative and which are intended to be used undiluted in first-aid or domiciliary treatment. The fact that the eye lotion does not contain an antibacterial preservative means that the solution, after opening, is limited to being used once only in first-aid treatment or within 24 hours in domiciliary treatment. There may be a case, however, for sodium bicarbonate eye lotion BPC to be so formulated that it can be used as a multiple dose preparation for domiciliary treatment.

Pseudomonas aeruginosa (*P. aeruginosa*) was stated to be the most common contaminant of aqueous solutions and the most lethal in its effect upon the eye (Allen, 1959). A survey of the literature revealed that the first report implicating contaminated ophthalmic solutions as the cause of *P. aeruginosa* corneal ulceration was that of Garretson and Cosgrove (1927). By the early 1950s it was fairly widely recognized that *P. aeruginosa* could be introduced to the eye as the result of using contaminated ophthalmic solutions (Bignell, 1951; Theodore, 1951; Theodore and Minsky, 1951; Allen, 1952; Theodore and Feinstein, 1952; Soet, 1952). The selected preservative system for ophthalmic solutions should therefore be capable of inactivating heavy contamination with *P. aeruginosa* as quickly as possible. It has been suggested that a sterilizing time of 1 hour or less is what should be expected of an antibacterial substance considered suitable for the preservation of ophthalmic solutions (Kohn, Gershenfeld, and Barr, 1963).

In an extensive review of the literature concerned with the preservation of ophthalmic solutions, however, it was concluded that "no single substance is entirely satisfactory for use as a preservative for ophthalmic solutions" (Richards, 1967a, b). It was suggested that anti-bacterial combinations offered possibilities of overcoming the problem and that the activity of such chemicals should be demonstrated against resistant bacteria.

Disodium ethylenediamine tetra-acetate (EDTA) was shown to accelerate the action of a quaternary ammonium compound against resistant strains of *P. aeruginosa* (MacGregor and Elliker, 1958). Consequently, the United States, National Formulary XII recommended the use of EDTA, with benzalkonium chloride, for the preservation of ophthalmic solutions. EDTA was shown to potentiate the activity of polymixin B. suphate, chlorhexidine diacetate and benzalkonium chloride against *P. aeruginosa* (Brown and Richards, 1965). Nevertheless there is no advantage in using EDTA in combination with phenylmercuric nitrate (PMN) to preserve fluorescein solutions (Brown, 1968). 2-phenylethanol (PEA), in combination with PMN, however, is a more effective preservative system for fluorescein sodium eye drops than the official BPC formulation, which is preserved with PMN alone (Richards, Suwanprakorn, Neawbanik, and Suraskidul, 1969).

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PEA was first recommended for use as a preservative for ophthalmic solutions by Brewer, Goldstein, and McLaughlin (1953). Other workers have found PEA to have too slow an antibacterial action for use in ophthalmic solutions (Kohn and others, 1963). It has been shown, however, that PEA exerts its antibacterial effect by modifying the permeability properties of the bacterial cell (Silver and Wendt, 1967; Richards and others, 1969), and so when used in combination with other antibacterials PEA can not only exert its own antibacterial action, but also enhance the action of the antibacterial with which it is combined (Richards and others, 1969). PEA is one of the four antibacterials recommended for preserving ophthalmic solutions in the USNF XIII 1970.

In view of the foregoing it was decided to investigate the efficiency of suitable antibacterials alone and in combination with EDTA, or PEA, for preserving sodium bicarbonate solutions against contamination with *P. aeruginosa.*

Chemical incompatibilities limited the choice of "suitable" antibacterials to benzalkonium chloride, chlorocresol, and PMN. Preliminary tests showed thiomersal to have no advantage over PMN and so thiomersal was not included in the extended tests.

Material and methods

The test organism used was *P. aeruginosa* strain NCTC 6750 and the growth medium for liquid cultures was Oxoid No. 2 nutrient broth. Oxoid nutrient agar was the solid culture medium. The inactivating medium used to prevent any carry over effect of antibacterial action consisted of thioglycollate medium USP, lecithin and polysorbate 80 (Riegelman, Vaughan, and Okumoto, 1956).

The sodium bicarbonate and the benzalkonium chloride were of BP quality and the chlorocresol, EDTA, PEA ann PMN were BDH laboratory chemicals. Cell numbers were estimated by colony counts as already described (Richards and others, 1969) and stock cultures were maintained as before (Brown and Richards, 1964).

PREPARATION OF THE SODIUM BICARBONATE EYE LOTIONS

The eye lotions were prepared by mixing aliquots of concentrated solutions of sodium bicarbonate and antibacterials before diluting to volume. The pH of the resultant solutions was measured before carbon dioxide was bubbled through for 1 minute. The solutions were then autoclaved at 121°C. for 20 minutes and the pH for each solution was determined within a short interval of opening the containers. A further series of pH determinations was made 3 weeks after opening the containers. Sterilization time determinations were made on the series of solutions immediately after autoclaving and on the series of solutions which were in the containers that had been opened and then left for 3 weeks.

DETERMINATION OF STERILIZATION TIME

9·9-ml. volumes of the different formulations were placed in metal-capped sterile test tubes and left to equilibrate in a water bath at 25°C.; 0·1 ml. overnight *P. aeruginosa* culture containing approximately 6×10^8 organisms/ml. was added to each tube. These inoculated solutions were designated reaction mixtures. At intervals of 15, 30, 45, 60, 90, 120, 150, 180, 240, and 300 minutes after the addition of the inoculum, 0·5-ml. samples were taken from each reaction mixture and added to 9·5 ml. of inactivating recovery medium and incubated for 3 days at 37°C. Positive controls to test the efficiency of the recovery medium consisted of 0·1 ml. of a 1 in 100 dilution of the overnight culture added to tubes of recovery medium separately containing 0·5 ml. of the different formulations. Samples of doubtful cultures were incubated on a milk agar medium to check for possible pigment formation and clearing of casein (Brown, 1968).

To ensure uniform suspensions of bacteria a vortex mixer was used to disperse the overnight culture, to disperse the inoculum in the reaction mixtures, to resuspend the organisms before sampling the reaction mixtures, and to disperse the sample of reaction mixture throughout the inactivating recovery medium.

Results

The results of the pH determinations and the survival time determinations are collated in the Table.

Table *Sterilization times for 3·5 per cent. w/v sodium bicarbonate solutions contaminated with* P. aeruginosa

Concentration of antibacterial(s)	*pH* *Before carbonating and sterilization*	*After sterilization*	*3 weeks after sterilization*	*Sterilization time (min.)* *At lower pH inoculum 5·4* $\times 10^6$*/ml.*		*At higher pH inoculum 7·4* $\times 10^6$*/ml.*	
0·01 per cent. w/v Benzalkonium chloride+	8·10	7·65	9·55	>30	<45	>15	<30
0·01 per cent. Benzalkonium+ and 0·4 per cent. Phenylethanol (PEA)	8·13	7·70	9·65	>15	<30	<15	
0·01 per cent. Benzalkonium+ and 0·05 per cent. Sodium edetate* (EDTA)	8·05	8·10	9·70	>30	<45	<15	
0·002 per cent. Phenylmercuric nitrate (PMN)	8·08	7·75	9·68	>180	<240	>45	<60
0·002 per cent. PMN and 0·4 per cent PEA	8·12	7·55	9·65	>45	<60	>15	<30
0·02 per cent. PMN and 0·05 per cent. EDTA	8·03	7·60	9·72	>150,	<180	>45	<60
0·05 per cent. Chlorocresol	8·08	7·55	9·65	>15	<30	>30	<45
0·05 per cent. Chlorocresol and 0·4 per cent. PEA	8·10	7·55	9·62	<15		<15	
0·05 per cent Chlorocresol and 0·05 per cent. EDTA	8·02	9·00	9·65	>30	<45	>15	<30
0·4 per cent. PEA	8·12	7·55	9·60	>240	<300	>30	<45
0·05 per cent. EDTA	8·10	7·55	9·65	>300		>300	

Controls: Duplicate controls separately containing 0·5 ml of each formulation plus 9·5 ml inactivating recovery broth were inoculated to a final concentration of approximately 6×10^4 overnight cells/ml. All gave growth
+A fine white precipitate was noted in all tubes containing benzalkonium chloride
*Sodium edetate—a synonym for disodium ethylenediamine tetracetate

From the pH readings it can be seen that bubbling carbon dioxide through the different formulations for 1 minute before sealing the containers was effective in lowering the pH of the solutions. The high pH, after autoclaving, of the chlorocresol and EDTA combination would indicate that the seal of the container was inadequate for that container. The pH of all formulations increased on storage. This in fact would be the case if the eye lotion was used as a multi-dose preparation. At the higher pHs the sterilization times were less than those determined at the lower pHs. The exception to this was chlorocresol alone which had a longer sterilization time at the higher pH. This was expected as the higher pH would ionize the chlorocresol and reduce its activity. The activity of benzalkonium chloride is known to increase with increasing pH but the fact that a fine white precipitate was formed in all formulations containing benzalkonium chloride indicates that benzalkonium chloride cannot be used for preserving these solutions.

PMN in combination with PEA is again shown to be a more effective preservative system than PMN alone, and PMN in combination with EDTA is again shown to be a less effective preservative system than PMN alone, thus confirming the results already mentioned (Richards and others, 1969; Brown, 1968).

Chlorocresol is shown to have a very rapid action even at the high pH. Chlorocresol in combination with PEA has the shortest sterilization time of all the possible formulations at both pHs.

CONCLUSION

These results would indicate that it is possible to adequately preserve sodium bicarbonate solutions against contaminations with *P. aeruginosa.*

Summary

The rationale behind using preservative combinations for the preservation of ophthalmic solutions is given.

Formulations of 3·5 per cent. w/v sodium bicarbonate solutions were tested for their ability to sterilize high inocula of *P. aeruginosa.*

Sodium bicarbonate 3·5 per cent. w/v solutions preserved with a 0·002 per cent. PMN/0·4 per cent. PEA combination had a sterilization of less than 1 hour.

Formulations preserved with either 0·05 per cent. chlorocresol alone or a 0·05 per cent. chlorocresol/0·05 per cent. EDTA combination sterilized in less than 45 minutes.

Solutions preserved with a 0·05 per cent. chlorocresol/0·4 per cent. PEA combination sterilized in less than 15 minutes.

Therefore the preservative systems in all these formulations quoted, when challenged with high inocula of *P. aeruginosa,* satisfied the requirement that a preservative suitable for preserving ophthalmic solutions should be capable of sterilizing contamination in less than 1 hour.

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Tonometry and tonography in the diagnosis of chronic simple glaucoma

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Tonometry has long been considered a satisfactory and accurate aid to the diagnosis of chronic simple glaucoma and, since the publication of a paper by Grant (1950), tonography has been acclaimed as a useful additional refinement. The results of tonography have been expressed either alone as an indicator of facility of aqueous outflow (C) or combined with a measure of intraocular pressure (Po) and expressed as Po/C, the coefficient of outflow.

Many of the observers who have confirmed Grant's findings have failed to state clearly their criteria for the diagnosis of chronic simple glaucoma. For example, Tuovinen (1961) implied that the diagnosis was, in part, based on tonometry and tonography, so that his argument about the effectiveness of the tests depends on the prior assumption that the tests are effective.

We will show that confidence in the results of tonometry and tonography is misplaced, especially in those reports in the literature, for example Paterson (1966), where these measurements taken at certain levels are accepted as diagnostic of chronic simple glaucoma.

Previous studies of tonography should have warned us against this practice. Gloster (1966) found that in 108 normal eyes all exceeded 0·12 in C value, and only 4 per cent. had values lower than 0·15. His experience in thirty glaucomatous eyes showed that the tests were less discriminating. C values were higher than 0·12 in 73 per cent. and higher than 0·15 in 54 per cent.

In our study we have made tonometric and tonographic observations and calculated the coefficient of outflow in four groups of eyes: non-glaucomatous, 'suspicious', untreated glaucoma, and treated glaucoma.

Criteria for diagnosis

CHRONIC SIMPLE GLAUCOMA

(1) Cupping of the optic disc
and (2) Visual field loss of a glaucomatous type
and (3) An open anterior chamber angle

We should regard an eye as 'suspicious' if it showed:

(1) Cupping of the optic disc
or (2) Visual field loss of a glaucomatous type
or (3) The fellow eye was glaucomatous

In no case has our diagnosis depended on a numerical value of tension or outflow. We have relied on clinical methods, including ophthalmoscopy, gonioscopy, and detailed

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examination of the visual fields. This latter test was carried out at 2 metres distance, normally with a 2 mm. white object or with the smallest target which permitted the patient to give accurate and reproducible replies.

The number of eyes examined was 855, in 451 individuals.

Results

Table I shows that the means of all our observations fall neatly into place.

Table I *Means of Po, C value, and Po/C in four groups of eyes*

Group	*No. of eyes*	*Po*	*C value*	*Po/C*
Nonglaucomatous	617	17·7 ± 0·17	0·28 ± ·005	83·2 ± 2·5
'Suspicious'	95	20·7 ± 0·56	0·20 ± ·011	153·4 ± 13·2
Glaucoma Untreated	49	23·2 ± 1·07	0·18 ± ·016	165·4 ± 21·9
Treated	95	21·8 ± 1·27	0·19 ± 0·23	163·2 ± 17·5

The results in the four groups of eyes show a relationship to each other that we should expect from the propositions that glaucomatous eyes have higher intraocular tensions and lower outflow facilities and coefficients of outflow than do normal eyes.

The eyes in our 'suspicious' group are intermediate between the non-glaucomatous eyes and the glaucomatous eyes, and the glaucomatous eyes under treatment show a tendency towards normality.

All this is well known. Some of the differences are not very great and of course refer only to the large groups of eyes which were examined. The danger of arguing from the means of these groups to individuals will be seen from the rest of the results.

Table II shows a summary of the measures of intraocular pressure at two levels of P_o which have been traditionally used to discriminate between non-glaucomatous and glaucomatous eyes. It will be seen that although there are large and statistically significant differences between these two groups of eyes, neither level discriminates so sharply that, from Po value alone, could an eye be allotted to one group or another. In the case of the glaucomatous eyes the distinguishing power is so poor that all the eyes would have to be examined by ophthalmological means.

Table II *Distribution of intraocular pressure (Po) in four groups of eyes, above two threshold levels*

Group	*No. of eyes*	*Po*	
		>21	>24
Nonglaucomatous	617	134 (21·7 per cent.)	52 (8·4 per cent.)
'Suspicious'	95	45 (47·4 per cent.)	32 (33·7 per cent.)
Glaucoma Untreated	49	30 (61·2 per cent.)	19 (38·8 per cent.)
Treated	95	59 (62·1 per cent.)	42 (44·2 per cent.)

Table III shows a summary of measures of outflow facility at three levels which have commonly been considered to be significant. A C value of less than 0·12 is very unlikely to be found in a normal eye, but it is not very likely to be found in a glaucomatous eye either. Again, in spite of the differences between the means of the groups, C value does not distinguish clearly between individual glaucomatous and normal eyes.

Table III *Facility of outflow (C) in four groups of eyes, below three threshold levels*

Group	*No. of eyes*	*C value*		
		< ·12	< ·15	< ·20
Nonglaucomatous	617	34 (5·5 per cent.)	64 (10·4 per cent.)	166 (26·9 per cent.)
'Suspicious'	95	19 (20·0 per cent.)	31 (32·6 per cent.)	50 (52·6 per cent.)
Glaucoma Untreated	49	6 (12·2 per cent.)	19 (38·8 per cent.)	35 (71·4 per cent.)
Treated	95	25 (26·3 per cent.)	46 (48·4 per cent.)	61 (64·2 per cent.)

Table IV shows a summary of coefficients of outflow at two different levels. This index gives us no great power to discriminate glaucoma from non-glaucoma than do the other two.

Table IV *Coefficient of outflow (Po/C) in four groups of eyes, above two threshold levels*

Group	*No. of eyes*	*Po/C*	
		> 100	> 150
Nonglaucomatous	617	173 (28·0 per cent.)	69 (11·2 per cent.)
'Suspicious'	95	54 (56·8 per cent.)	35 (36·8 per cent.)
Glaucoma Untreated	49	37 (75·5 per cent.)	20 (40·1 per cent.)
Treated	95	62 (65·2 per cent.)	50 (52·6 per cent.)

Discussion

We have shown that, using generally accepted critical levels of tonometry and tonography, there is so much overlap of measurements that these tests are rendered useless as aids to diagnosis of chronic simple glaucoma in individual cases. It is obvious that there is serious danger in using either of these tests alone, or in using the two combined. The number of false negatives means that many patients with clinical glaucoma will be left untreated, and the number of false positives means that many who have normally functioning eyes, will be subjected to unnecessary treatment.

We have applied the numerical diagnostic criteria of Paterson (1965) (a pressure of over 25 mm. Hg on the applanation tonometer and a reduced outflow value—Po/C greater than 100) to our non-glaucomatous eyes and our 'suspicious' eyes. We found, in the non-glaucomatous group, that this would reclassify 33 of them as glaucomatous. In the 'suspicious' group, it would reclassify 25 of them as glaucomatous. Only one of these 58 patients had any sign of field defect.

Even as screening tests, these procedures are highly unsatisfactory. There is no critical level in these tests which would not result in the referral of an intolerable number of false positive cases for ophthalmological examination and none that would not allow an unacceptable number of patients with untreated glaucoma to be sent home in the belief that their eyes were healthy.

Fig. 1 shows the distribution of C values in our cases with its large overlap rendering the test insufficiently discriminating. Alongside is an ideal distribution showing a hypothetical test in which discrimination is good (Fig. 2).

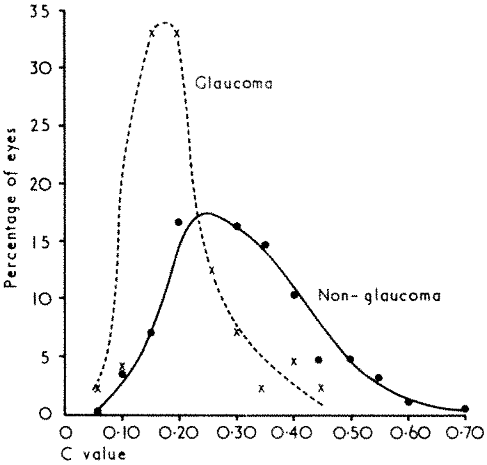

FIG. 1 *Distribution of C values in glaucomatous and non-glaucomatous eyes*

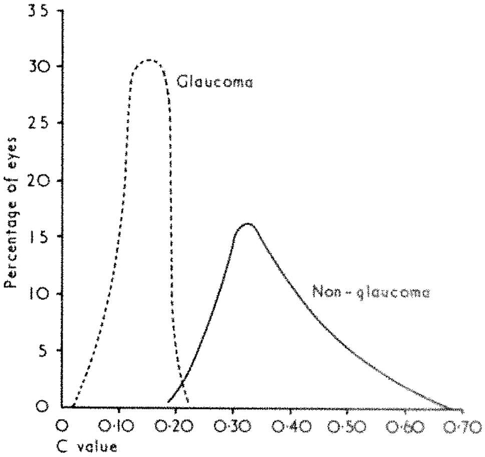

FIG. 2 *Hypothetical distribution of C values to allow good discrimination*

We believe we have shown that tonometry and tonography unsupported by full clinical ophthalmological examination cannot be used for the diagnosis or the elimination of chronic simple glaucoma. It is not our intention to comment here on the usefulness or otherwise of these tests in the assessment of the progress of the disease or of the results of treatment.

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Demodex folliculorum and oedema of the eyelash

F. P. ENGLISH

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In 1842 the Frenchman Berger discovered the mite *Demodex folliculorum* and later introduced this parasite to medical science (Berger, 1845). After more than a century of sporadic literature on this topic, there has been a resurgence of interest in ophthalmology triggered off by a stimulating thesis on *Demodex folliculorum* blepharitis (Coston, 1967).

Belonging to Class Arachnida, Order Acarina, *Demodex folliculorum* can infest the eyelashes, hair, and meibomian and sebaceous glands of man. The adult (Fig. 1) is vermiform in appearance, measuring 280 μ in length in the male, 270 to 440 μ in the female, and can be found in great numbers in the hair follicles. Possessing a well-developed prostoma and biting apparatus, the octopod *Demodex folliculorum* is characterized by distinctive annular markings on the abdomen. The legs, though rudimentary, are quite active and when placed on a microscope slide the parasite demonstrates an impressive degree of mobility. The clinician can readily demonstrate this property *in vivo* by causing evacuation of the hair follicle when the skin surface is stimulated with an irritating agent such as ether. Even so, in the presence of the bright light of the biomicroscope, complete evacuation does not occur, as the head appears photosensitive, and the observer becomes aware of its presence only by the sight of a number of cream-coloured tails protruding from the lid margin like fine bristles.

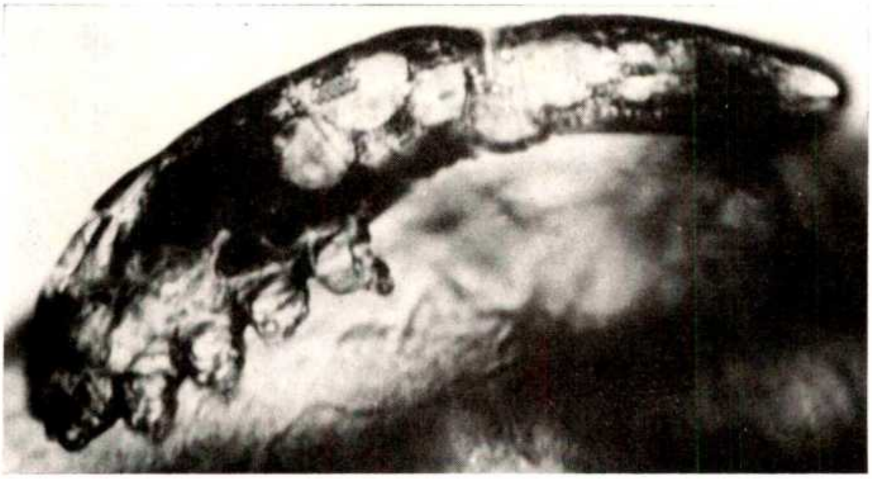

FIG. 1 *Adult* Demodex folliculorum *located on an eyelash.* ×425

(Courtesy of the *Medical Journal of Australia:* English, 1969)

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The immature adult is more slender in appearance, often longer than its later counterpart and quite inactive. The shield-shaped egg has been measured by Gmeiner (1908) as 0·08 mm. in length and 0·04 mm. in width. In searching for the parasite an epilated lash is placed in a peanut oil preparation on a microscope slide. Careful scrutiny with light microscopy may reveal the whole gamut of development from the egg, through larval, protonymph, and deutonymph, to the adult stage.

Where heavy infestation of the eyelids occurs, accumulation of mite faeces produces a distinctive cuff of plastic-like material around the eyelash. The parasite has also been described in the meibomian gland and in chalazion formation, and is believed responsible for pityriasis folliculorum and a type of acne rosacea (Coston, 1967). A variable incidence has been recorded throughout the world; and this often depends on the number of eyelashes epilated and the experience of the observer in the technique of examination.

Other demodectic mites can infest mammals, including *Demodex bovis* in cattle, *Demodex cati* in cats, *Demodex phylloides* in pigs, and *Demodex canis* in dogs. The last mentioned is of interest as it causes red mange in dogs and morphologically appears similar to *Demodex folliculorum*.

The study of the eyelash is one which has received scant consideration from ophthalmic researchers. Considering the intimate and prolonged association of *Demodex folliculorum* with the hair follicle, it is interesting to consider if it has any deleterious effect on the cilia. From the following observations it appears that the presence of this acarid is responsible for disease of the eyelash.

Methods and material

An epilated cilium noted to have a single adult *Demodex folliculorum* parasite adherent to the hair bulb was fixed in 4 per cent. glutaldehyde solution and embedded in epoxy resin. Many sections 0·5 μ in thickness were cut and the specimens studied.

Results

The section performed in the zone of parasitic adherence corresponded with the distal portion of the bulb of the eyelash. At the site corresponding with the original area of attachment was a well-defined region showing distinctive pathological features: marked intercellular oedema with teasing out of the cellular components (Figs 2 and 3, overleaf) and associated with the localized area of hydrops was hyperproduction of the hair keratin.

In reviewing a large series of chronic cases of demodectic infestation of the eyelids, this observer has sometimes noted an alteration in the physical character of the eyelashes. An epilated cilium is held with a fine pair of forceps and briskly tapped end-on against a solid surface, such as the anaesthetized cornea or conjunctiva. A healthy eyelash will display a somewhat vibrant character readily resuming its normal configuration (Fig. 4). This resilence is not unexpected in view of the term vibrissa, which is used for such hairs.

In demodectic infestation, however, the cilium fails to possess this expected property, and tapping produces a crumpled effect similar to that expected to be seen if one substituted a strip of moistened blotting paper (Fig. 4, overleaf). The earlier mentioned hydropic features of the disordered cytoarchitecture of the cilium appears to explain the soggy or waterlogged nature of the eyelash.

A survey was made of a series of 100 eyelashes from two groups of adult patients, the first exhibiting the presence of the acarid and the second free from parasites. There were five patients in each group and ten cilia were taken from each subject.

(2)

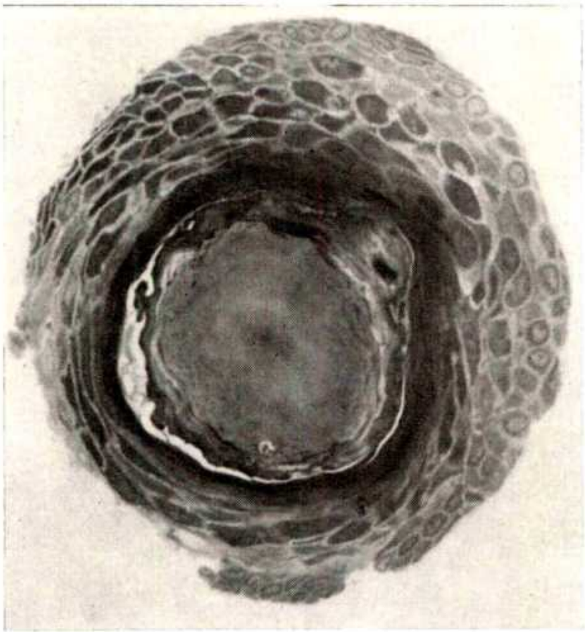
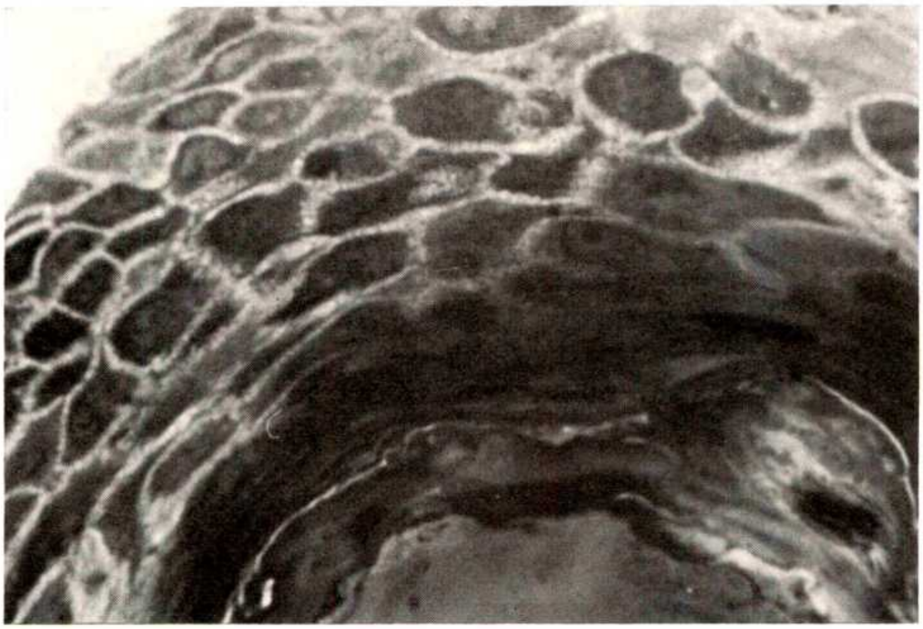


FIG. 2 *Cross-section of eyelash, displaying pathology at original site of adherence and located strictly to one side of the bulb.* × 192

FIG. 3 *Higher magnification, demonstrating oedema of eyelash with teasing out of the cellular elements.* × 850

(3)



In the group with no infestation 46 (92 per cent.) of the fifty eyelashes showed normal resilience, and four (8 per cent.) were diseased. In this group it would be difficult to rule out previous contact with this commonly occurring mite.

In the group with established parasitization 62 per cent. of the eyelashes were healthy, and 38 per cent. were abnormal. It would appear therefore that soggy eyelashes generally indicate the presence of an associated concomitant demodectic infestation.

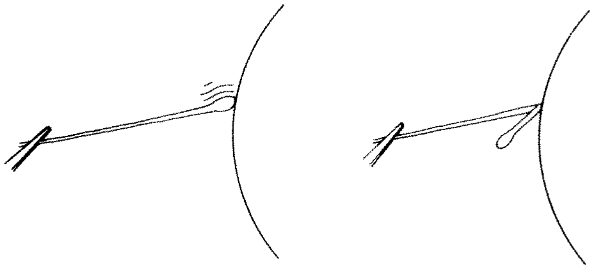


FIG. 4 *Diagrams showing normal resilience of healthy cilium (left), and crumpled effect on diseased soggy eyelash (right)*

Comment

It should be pointed out that this particular case is representative of mild parasitization as only one mite is involved. It is possible for twenty or more acarids to cling to one eyelash, and so cause much more severe damage.

A number of factors may be involved in the oedematous process affecting the eyelash. The incidence in the community varies Jacobsen (1969), in New York City, recorded that as many as 40 per cent. of his adult patients were affected. Living in the repository of the follicle they enjoy close proximity to the body of the eyelash and specimens often appear adherent to the hair. The adult possess well-developed powers of locomotion and its activity is believed to be diurnal. The immature elongated form does not appear to shift from its position of lodgement and thus exerts a prolonged effect on the nutrition of the cilium.

At present there are gaps in our knowledge of the physiology of digestion of the acarids. Demodectic mites possess a voracious appetite and enjoy a diet of sebum; it is possible that the combination of potentially irritating lipolytic enzymes combined with the well-developed biting apparatus initiates the cycle of ingestion and plays a role in disease of the hair.

In earlier studies of the ultrastructure of this mite a vector capacity for bacterial infection was established (English, Iwamoto, Darrell, and De Voe, 1970). The presence of micro-organisms on the integument of the parasite may also be responsible for enzyme production which reacts adversely on the nutrition of hair.

Symptoms of irritation result from the accumulation of mite excreta and eventually the shaft of the lash may be insulated with foreign material. Extension can even advance past the eyelid border producing the classical cuffing seen in advanced cases. It is difficult to ascertain whether this material plays a role in softening the shaft. If so, a considerable length of the eyelash would be exposed to a potentially noxious agent.

A careful study of a large series of cases over the last decade, has given Coston (1969) the clinical impression that in long-standing infestation with *Demodex folliculorum* some loss of the eyelashes may result. The present histopathological findings of the diseased soggy eyelash appear to be consistent with his observations. This is further borne out by the relative ease with which these lashes may be pulled out, there being virtually no resistance. Finally, on a wider scale, it is interesting to consider the likelihood that body hair oedema produces shedding of hair in alopecia. In this context it is of note that Hirst (1919) mentioned of a report that his brother, who was bacteriologist of the General Military Hospital, Alexandria, reported finding numerous specimens of this parasite in scalp disease simulating alopecia areata.

I am indebted to Dr. Tochiro Kuwabara for his histopathological study and report, to Mr. Max Irwin for the preparation of numerous sections, to Dr. Claus Dohlman for helpful advice, and to the Editor of the *Medical Journal of Australia* for permission to reproduce Fig. 1.

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Variant of *Demodex folliculorum* infesting the eyelids

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The mite *Demodex folliculorum*, which is currently evoking interest amongst ophthalmologists throughout the world, has been thoroughly described in detail by Coston (1967), Smith and McCulloch (1969), and English (1969).

Mites and ticks, in contradistinction to the other arachnids have fused segments, giving a characteristic morphological appearance. Accordingly, the adult type of *Demodex folliculorum* presents a vermiform or cigar-shaped profile (Fig. 1) with a well differentiated prosoma incorporating head and thorax, and an opisthosoma consisting of abdomen and tail ending in a smoothly rounded off caudal extremity. The segmented thorax bears four paired appendages and the abdomen is distinguished by annular markings or grooves. This latter feature possibly is a type of dermatoglyphic adaptation to its follicular environment, allowing for its facility of ready ingress or egress.

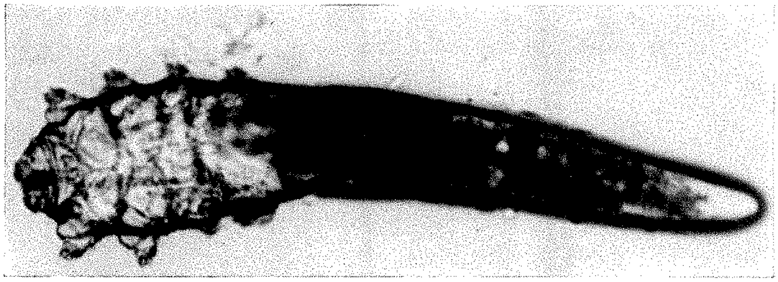

FIG. 1 *Ventral view of adult specimen of* Demodex folliculorum. × 400 (Courtesy of *The Medical Journal of Australia*: English, 1969)

A variant of *Demodex folliculorum* can sometimes be found in the eyelids, and this may lead to confusion in identification of the infesting organism and a mistaken diagnosis.

Methods and materials

In reviewing an elderly male patient suffering with blepharitis parasitica of demodectic aetiology, an unusual variant was observed when the eyelashes mounted in a peanut oil medium were subjected to microscopic examination.

Observations

One microscopic slide (Fig. 2, overleaf) displayed the whole range of the life history of the parasite passing from the egg through the immature to the adult stage and also contained the interesting caudate variant, located near the bulb of the eyelash.

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(2)

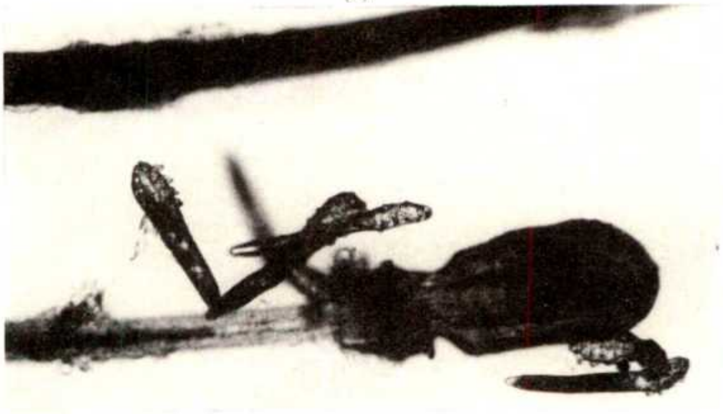

FIG. 2 *Range of presentation of* Demodex folliculorum, *the egg, and the immature and adult stages. The short variety is located near the bulb of the eyelash.* ×60

(3)

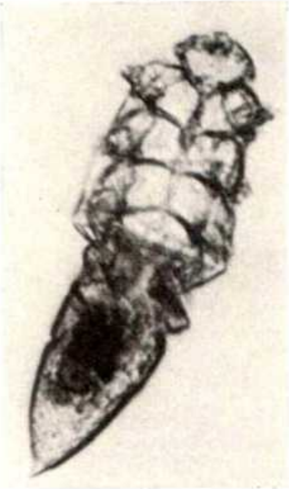

FIG. 3 *Ventral view of caudate or short type of* Demodex folliculorum. ×250

Higher magnification (Fig. 3) reveals this variant to have an overall stumpy appearance with a short abdomen, characterized by a pointed caudal extremity.

The capitulum is mature in development and segmentation of the thorax is well defined. The characteristic annular banding of the abdominal wall is absent.

The overall body length is three times the width of the cephalothorax, whereas in the normal long type this may be seven times the width of the cephalothorax. The abdomen was approximately the same length as the cephalothorax, whereas in the normal type, it may be two and a half times as long as the prosoma. The short parasite was not as active as the larger form.

Comment

Demodectic mites enjoy a wide distribution throughout the animal kingdom, parasitizing the sebaceous glands and hair follicles of most mammals. The varieties encountered and their respective hosts include *Demodex canis* (dog), *Demodex cati* (cat), *Demodex phylloides* (pig), *Demodex bovis* (cattle), *Demodex equi* (horse), *Demodex muscardini* (dormouse), *Demodex cuniculi* (rabbit), *Demodex ratti* (rat), and numerous others. Much study has been devoted to differentiating these different species. The proportions of the body, the nature of the dorsal spines of the capitulum, the location of the male genitalia, and the structure of the ova are some of the important distinguishing characteristics of value to the acarologist.

When first observed the appearance of the caudate variety of *Demodex folliculorum* may be quite misleading, and it can readily be misidentified as *Demodex phylloides* which it closely resembles. Such a conclusion may lead one to rationalize, quite erroneously, that this feature confirms the disputed theory of cross-transmission of demodectic mites.

Demodex phylloides, which is responsible for demodectic mange in pigs, is a short acarine measuring up to 230 μ in length, rather wide, with a total length about three and a half times the width of the cephalothorax. Like the caudate variety of *Demodex folliculorum* it ends in a narrow tail-like process. It differs in having a banded abdomen and the male genital orifice is located dorsally in a more anterior position between the first and second legs.

Demodex equi may also be a source of confusion when the posterior end of the abdomen is bluntly pointed. Often, however, it is smoothly rounded off and presents no problem in differentiation. In passing, it is interesting to note that the affected patient enjoyed a variety of occupations true to the egalitarian background of Australian society. These ranged from whisky dealer, salesman, and company manager to horse trainer. In this last mentioned context the potential of the infesting organism was of particular interest.

According to Hirst (1919) we are indebted to the studies of Erasmus Wilson (1844), that astute lecturer in anatomy and physiology of the Middlesex Hospital, London, who was responsible for the elucidation and description of the caudate variety of *Demodex folliculorum* in the 19th century.

Shortly after Simon (1842) produced his paper on *Demodex folliculorum*, Wilson devoted his full energies to the study of this parasite which he preferred to call *Entozoon folliculorum*. In his exhaustive investigations he came across the short form which he was able to differentiate and classify. He concluded that, during development, the common type passes through an intermediate form which does not apply to the short variety. He draws an interesting analogy with a similar modification seen in the common earth worm.

Wilson's studies permit an exact differential diagnosis from other species particularly those found in swine and horses, and assist the ophthalmologist in recognizing the various forms of *Demodex folliculorum*.

I am indebted to Prof. William Nutting of the University of Massachusetts, Amherst, and to Dr. Robert Domrow, acarologist, Queensland Institute of Medical Research, for their assistance in helping to differentiate this organism, and to the Editor of *The Medical Journal of Australia* for permission to reproduce Fig. 1.

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Brit. J. Ophthal. (1971) **55**, 750

Lid changes in non-bullous ichthyosiform erythrodermia

H. M. ROSE
Liverpool

Ichthyosis is a condition in which the skin shows visible removable cutaneous scales (Wells, 1966). It is due to a disturbance of the normal balance between formation and desquamation of skin keratin.

Ocular changes reported in ichthyosis are blepharitis, hypertrophic conjunctivitis, corneal vascularization, ectropion, lagophthalmos, and keratitis (Cordes and Hogan, 1939), corneal nodes (Vail, 1940), and cataracts, optic atrophy, and retinitis pigmentosa (Stewart, 1939). Most writers have described single cases. Jay, Blach, and Wells (1968) analysed the ocular features of 62 cases, and found that lid and certain corneal changes were characteristic of the disease, while other changes were secondary or coincidental.

The disease was classified into four groups on genetic and clinical grounds by Wells (1966).

The present paper reports three cases of the type called "congenital non-bullous ichthyosiform erythrodermia", which is characterized by the following features:

(*a*) autosomal recessive inheritance;

(*b*) presence at birth;

(*c*) congenital erythrodermia (which fades later);

(*d*) scaliness of the upper face, flexures, palms, and soles;

(*e*) worsening with age.

The patients were three siblings, two of whom showed, at the age of 2 weeks, ectropion of the upper lids with, in one eye, lagophthalmos without ectropion, caused by stiffness of the skin of the lids. There is no family history of ichthyosis, and the parents are not consanguineous.

Case reports

(1) *Tony* (Date of birth February 10, 1970).

This baby was first seen by an ophthalmologist at the age of 2 weeks. At birth he had the appearance of being encased in a tight red collodion membrane, which was the thickened horny layer of epidermis. Fissures appeared in the skin surface, dividing it into peeling scaly areas in which the skin was dry, firm, inelastic, paper-smooth, and brittle.

Fine fissures radiated from the outer canthi. There were no horizontal creases in the lids, presumably because movements were impaired by stiffness; there were however some obliquely vertical fine folds (along which the surface was cracked) in the upper lids, such as might result from upward traction in attempts at elevation. There was no blinking and no closure in sleep, and the lids

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remained half open at all times except with activity of the orbicularis in crying (Fig. 1). The right upper lid was tented and its tarsal conjunctiva everted. When the right upper and lower lids were approximated, the margin of the upper rode in front of the lower. For the first 2 days after the eyes were examined, there was a small discharging abscess in the middle of the margin of the right upper lid. The associated swelling did cause closure of the lids, but when this had subsided, the right eye remained open again.

The left upper lid was not everted, but the left eye remained continuously open.

Only a few very fine short lashes were present. The puncta were normal.

The anterior segments of the globes were normal.

Conjunctival swabs grew staphyloccoci, sensitive to neomycin. Neomycin was instilled 4-hourly.

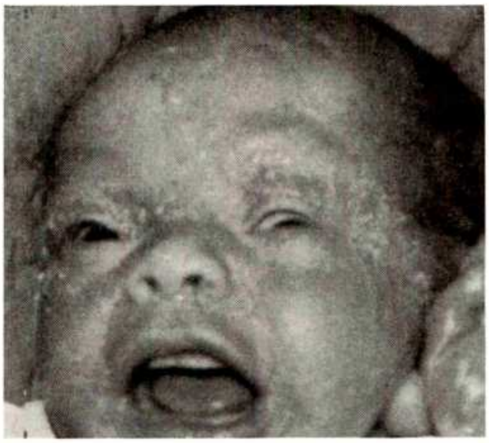

FIG. 1 *Case* 1 *at* 2 *weeks. Eversion of right upper lid with exposure of conjunctiva*

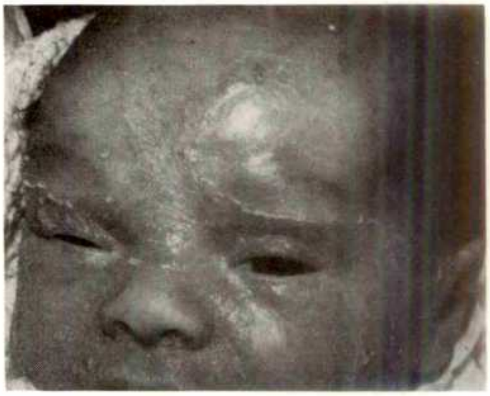

FIG. 2 *Case* 1 *at* 3 *weeks. Over-riding of right lower lid by right upper lid*

At this stage it was thought that the ectropion of the right upper lid was likely to increase and cause permanent exposure of the eye, with conjunctival and corneal changes. It was decided to do a tarsorrhaphy to correct the deformity and protect the globe.

After a further week, however, the lids appeared more active and there was some blinking to light, though with rather slow stiff motion and with only orbicularis action. The right upper lid was less everted and the tarsal conjunctiva was less exposed (Fig. 2). The cornea was clear. The eye still did not close fully except in crying. Operation was deferred.

A few days later (the baby being now one month old), the right upper lid was in normal apposition to the globe with no eversion. Lid movements were still better and the eyes closed in sleep. Under mydrilate, the media and fundi appeared to be normal.

During this period the condition of the skin generally improved: the original dry hard horny layer was shed in scales, revealing softer, more flexible, though still ichthyotic, skin underneath. From this time onwards the skin was treated with an ointment containing vitamin A acid, which has been recently used for various dyskeratotic skin conditions (Fulton, 1968).

(2) *Jacqueline* (Date of birth August 21, 1967)

This child had severe congenital ichthyosis. When seen at 16 days of age, she had ectropion of both upper lids, and a lateral tarsorrhaphy was done in the right eye and lateral and medial tarsorrhaphies in the left.

There was considerable infection, with an abscess in the left upper lid; all subsided with neobacrin ointment and chloramphenicol drops.

Now, at the age of 2½ years, the lids have flexible skin with normal movements. There is a residual 3 mm. of lateral tarsorrhaphy in the left eye. There are a few matted lashed in the upper lids, and none in the lower.

This child shows severe mental ratardation as well as ichthyosis: she cannot walk or speak, and has a left hemiplegia with deformities of the left hand and foot. The eyes show course nystagmoid movements, and although she sometimes looks towards objects and follows a light, there is marked lack of attention. The anterior segments, media, and fundi are normal.

(3) *Joseph* (Date of birth September 21, 1968).

This child has mild ichthyosis with normal lids and eyes, and in mentally normal.

Comment

Jay and others (1968) point out that the only type of ichthyosis in which ectropion occurs is non-bullous ichthyosiform erythrodermia. In their cases and those of previous writers (Hudson, 1926; Cordes and Hogan, 1939; Vail, 1940; Stewart, 1939), ectropion is described as affecting the lower lids, and as developing secondarily to contracture.

The cases described here are of a different nature:

(1) The ectropion affected the upper lids, occurred neonatally, and was not progressive, even resolving spontaneously in one case;

(2) One eye showed lagophthalmos without ectropion, because of stiffness of the skin of the lid. In spite of some weeks non-closure, no corneal changes occurred.

The spasticity and mental retardation in the older child suggests comparison with the Sjøgren-Larsson syndrome (Wells, 1966) and the syndrome of Rud (Stewart, 1949), although there were no lens or retinal changes.

I should like to thank Dr. F. Hudson who referred the patients; and Mr. Alan Patterson for suggesting that this paper should be written.

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Effects on employment of defects in colour vision

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The more information which can be fed into a computer the greater its power; similarly we are more efficient as individuals the finer our sense of touch, the greater the range of sounds we can hear, or the closer that two points can be detected separately by the eyes. The finer the discrimination the wider is the information available for action by the intellect. This then is the measure of the value of a fully developed colour sense.

So far as colour is concerned, a majority of people (the trichromats) are able to judge its hue by reference to a three-point standard which allows accurate discrimination of a large variety of hues. A small number*, however, just over 2 per cent. of boys and about 0·1 per cent. of girls (the dichromats) have only a two-point standard, and as a result the number of hues that can be discriminated is greatly reduced.

There is also another group, perhaps 4·5 per cent. of boys and 0·3 per cent of girls (simple anomalous trichromats) who, although possessing three-point standards, have these in unusual combination; so that, while perceiving a wide range of hues, they see them differently from the generality. Figs 1, 2, and 3 (after Farnsworth, 1947) express these differences diagrammatically. Such persons also find themselves unable to agree with colour matches accepted by most people, and in their turn make matches inacceptable to the majority.

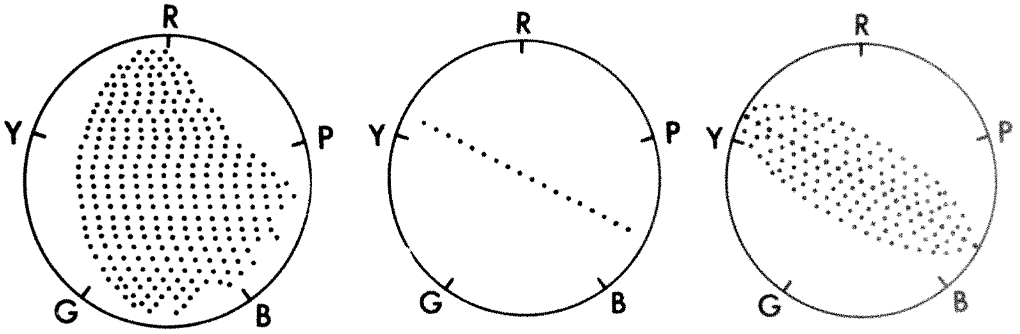

FIG. 1 *The wide range available to the normal*

FIG. 2 *The much reduced range available to the dichromat (in this case 'green blind')*

FIG. 3 *The intermediate range available to an anomalous trichromat (here 'green anomaly')*

FIGS 1 to 3 *Graphic representation of the separate hues discriminable at a particular level of brightness (after Farnsworth,* 1947: *originals copyright of the Psychological Corporation, New York)*

This forms the well-known hue triangle, but it must be remembered that it is only a section across a three dimensional figure, since greater or less brightness introduces a series of similar figures from light to dark, the whole forming the 'colour solid'. R = red, P = purple, B = blue, G = green, Y = yellow

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*The figures are given only as an approximation to indicate relative frequencies. But see Kalmus (1965), Chaps 4 and 5.

Yet another group (the extreme anomalous trichomats), say 1·5 per cent. of boys and 0·1 per cent. of girls, appears to be intermediate between these two, in that they see a diminished range of hues, and can match over a wide range (Fig. 4) which usually includes the matches made by 'normal' people.

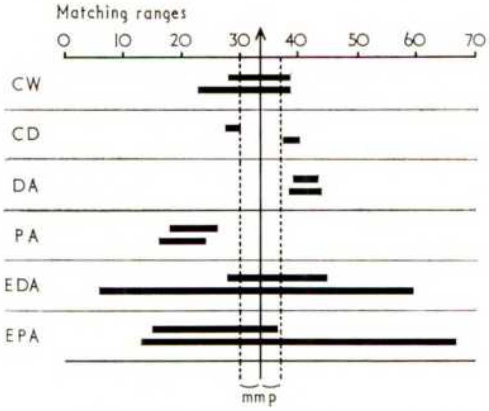


FIG. 4 *Matching ranges of various colour defects on a Pickford Anomaloscope*

A person with normal colour vision makes matches centred on the vertical line through 35·5 units (on this particular instrument), and the modal matching range is three units. The section marked mmp is the normal range of middle matching point (±2 S.D.)

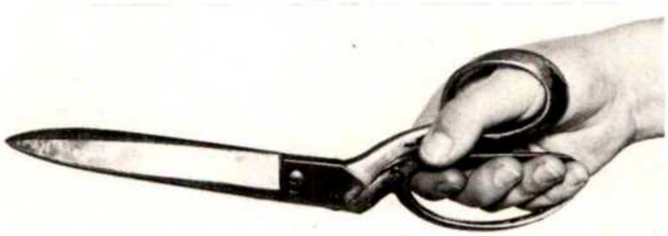
CW = Colour weak
CD = Colour deviants (these may be only the extreme limits of normal variation, which follows a Gaussian distribution)
PA = Simple protanomaly
DA = Simple deuteranomaly
EDA = Extreme deuteranomaly
EPA = Extreme protanomaly

Dichromats (whether green or red blind) of course match over the entire range from zero to 72

These different abnormal groups comprise almost one in twelve of the male population. It is clear that anything which reduces our power to tell different objects apart must be a handicap. What matters, however, is whether the handicap is a *significant* one, and in particular, whether it influences the ability to follow any particular occupation.

The handles of scissors are shaped to suit the right-handed persons who comprise the majority of the population (Figs 5 and 6) and are really quite awkward for the left-handed. Had the proportions of the left and right-handed in the population been the other way round, the scissors would have been shaped accordingly.

(5)



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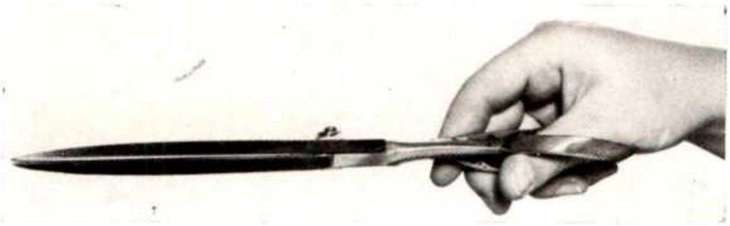

FIGS 5 and 6 *Scissors are for the right-handed*

Similarly, had 92 per cent. of the population used only a 2-colour system for detection of hue and the remaining 8 per cent. been a somewhat freakish group seeing differences where the 'normal' population saw none, then our use of colour in industry and commerce would have developed very differently. Probably a great deal more reliance would have been placed on the other variables, especially luminosity ('brightness').

Unfortunately for the 2-colour and the distorted 3-colour people, the world is *not* so constructed and they may thus be faced by material disadvantages. The commonest disability is the confusion of red and green, and these are precisely the colours most frequently used to indicate danger on the one hand and safety on the other. Instances of railway accidents due to such defects were found soon after the introduction of a signalling system (Wilson 1855); and Nettleship (1913), in a rather amusing little book, reviews the evidence. He quotes the case of a Swiss engine-driver in the 1870s who appears to have been colour blind. He had no great trouble while he had a normal fireman, but when he was joined by a colour-blind fireman, he was in trouble. This driver was able to distinguish green from white only by the greater brightness of the latter, while the red lamp was so difficult that its 'colour was almost undistinguishable until he was too near it to stop his engine' in time. He claimed to be able to imitate the three signal colours by turning the wick of his (oil) lamp more or less up or down, thus varying its brightness, while he compared it with the approaching signal. This would certainly not be possible at today's speeds. There is no record that he had any serious accident, despite his disability, although he was frequently fined for breaches of the regulations. It is strange that the authorities in most countries seemed reluctant to introduce legislation against this danger. Even after an accident had occurred and a question of misreading signals arose, no effort seems to have been made by the judiciary to check the colour vision of those testifying to the colour of the signal lamps displayed (and witnesses as well as those accused should of course be tested). Apart from reluctance by employers to lose, or to exclude otherwise suitable men, a major reason may well have been the lack of an easily applied and reliable test until comparatively recently.

Even in 1897, a man involved in an accident was examined by the Board of Trade with the inefficient Holmgren Wool test. It was not until the 20th century that simple tests of reasonable accuracy such as the Ishihara test became generally available.

However slow the acceptance of the dangers of colour defect may have been, it is not unlikely that modern techniques have increased the difficulties for the colour-blind. The use of colour-coding makes processes simpler or safer for the colour-normal but, unless they are specially thought-out with colour deficiency in mind, they make the former's task more difficult or impossible. The first necessity is to identify those at hazard.

Present investigations

Since 1962 this identification has been attempted in Scotland during the school years. The techniques employed (see Appendix) and the standards adopted have been given in previous papers (Taylor, 1966, 1970a) and will not be repeated here. Roughly 20,000 children have been tested by school medical officers in Ayrshire since 1963, most of them at routine school examinations at age 12 or 13, but some at other ages. Those failing an Ishihara test were then referred to my advisory clinic for full analysis.

Any child, whose colour vision was doubtful to either teacher or parent, was also seen; no accurate estimation of the frequency can be made since the underlying population is not precisely known, and some 2 to 5 per cent. each year failed to attend in spite of being given repeated opportunities.

Material

Between 1965, when this advisory clinic was started, and late 1970, 904 children were examined. Of these seventy had no significant colour defect whatever, and three had apparently a blue-yellow defect (not fully tested), leaving 831 (776 boys and 58 girls) with red/green deficiency. In all cases enquiry was made as to the career proposed, and advice was proffered as to what action should be taken after any defects had been diagnosed.

The distribution of defects is set out in Table I.

Table I *Type of colour defect, by sex*

Defect	*Male*	*Female*
P	107	1
EPA	40	2
PA	49	1
Colour blind		
D	153	15
EDA	102	7
DA	292	22
Colour weak	11	10
Low colour discrimination	18	10
Blue/yellow defect only	2	1

P = Protanopia (complete red blindness)
EPA = Extreme protanomaly (severe red blindness)
PA = Simple protanomaly (moderate red blindness)

D = Deuteranopia (complete green blindness)
EDA = Extreme deuteranomaly (severe green blindness)
DA = Simple deuteranomaly (moderate green blindness)

Colour weak—Middle matching point normal but range wide ("insensitive")

Low colour discrimination—Poor judgement of colours near each other in hue

The first group, 'colour-blind', contains those usually considered in this context, but the 'colour weak' and those with 'low colour discrimination' have also to be considered in the light of their future occupation.

The children's ages at the time of the examination ranged from 10 to 18 years, with about two-thirds being aged 13 or 14 years.

As would be expected the percentage who had decided on a future career increased fairly steadily with age (Fig. 7). About half were at the end of their primary schooling and the rest in their last year or so at secondary school.

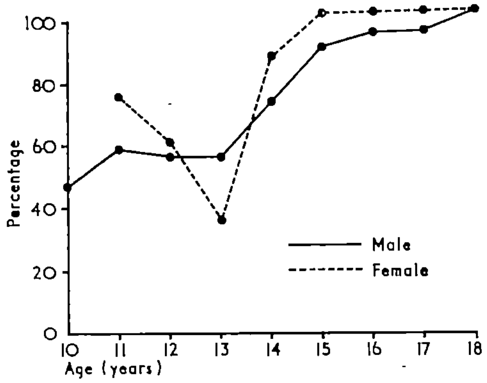

FIG. 7 *Percentage of colour-defective children, by age at examination, who had decided on a possible career*

Since colour blindness is rare in girls, the percentages in their cases may be distorted by the very small numbers. The 75 per cent. at age 11 represents three girls out of only four seen at this age.

Classification of careers

From those who had chosen, a division was made into "suitable" and "unsuitable", based on the recommendations of the Careers Bulletin of the Youth Employment Service, after due consideration of the degree of disability found in relation to the particular career suggested (Table II, opposite).

Table II *Choice of career, by age and sex*

Age (yrs)	*Male*		*Female*	
	Suitable	*Unsuitable*	*Suitable*	*Unsuitable*
10	3	12	—	—
11	14	15	0	3
12	16	20	3	7
13	42	55	2	1
14	86	164	4	9
15	22	31	3	6
16	5	9	—	—
17	9	18	2	1
18	2	4	1	0
Totals	199	328	15	27

The kinds of career considered unsuitable were then divided into those in which colour defect can be considered a minor handicap, a major handicap, or a definite bar (Table III).

Table III *Adverse effects of colour defects on choice of occupation*

Handicap						*Definite bar*
Minor (81)			*Major* (145)			
Agriculture	(*e.g.*	Gardener)	Agriculture	(*e.g.*	Fruit trials officer)	Navigation
Teaching	(*e.g.*	Geography)	Teaching	(*e.g.*	Chemistry)	Traffic control
Textile	(*e.g.*	Dressmaker)	Textile trade	(*e.g.*	Carpet designer)	Radio-telegraphy
Retail trade	(*e.g.*	Draper)	Retail trade	(*e.g.*	Butcher)	Electrical work (post-office and Railway
Service	(*e.g.*	Driver)	Service	(*e.g.*	Electrician)	Officer in Forces
Armed Forces	(*e.g.*	Artillery)	Armed Forces	(*e.g.*	Medical officer)	Police

Some careers, such as teacher, are too vaguely described and must be more exactly specified (Table IV), while others, although possibly containing elements where a colour defect would be a handicap—such as 'market gardener', should be more closely defined (Table IV), when it may be possible by eliminating the risk to follow the career after all.

Table IV *Careers requiring further definition*

Career not adequately specified (43)	*Exact task not specified* (56)
With animals	Farming
Teaching	Marine Engineering
A trade	Retail trade
A profession	Physicist

The Tables refer primarily to the degree of difficulty likely to be encountered in a particular occupation, which has then to be weighed against the subjects' degree of defect. The occupations quoted are by no means exhaustive, including only those suggested to me by the children. Of course, the career suggested by any boy is obviously strongly conditioned by what he believes to be available (quite apart from the cases in which he proposes to follow his father's occupation). For example, a boy living in Kilmarnock may choose to be a cooper because of the existence of a large firm of whisky distillers in his town.

Further examples may be obtained from the 'Report on Defective Colour Vision in Industry' (Physical Society, 1946) and the 'Careers Bulletin' of the Youth Employment Service (1966, 1968). Although 355 children had chosen an unsuitable career, 389 careers were involved, since 34 had given alternative (and also unsuitable) careers. A further ten children had given an alternative which *was* suitable.

Difficulties in the careers shown in the first two categories in Table III may be encountered even with fairly minor degrees of colour defect, although the particular occupation may still be possible, at a cost in extra effort. Awareness of the exact nature and extent of the defect is of material assistance to this end. It is also to be remembered that what is a major handicap during the training period may only be of minor significance once the individual is trained—it may be possible to avoid branches of an industry in which the defect is vital—such as to avoid specializing in skin disease if one is a doctor of medicine; to use instrumental methods to detect colour end-points if one is a chemist; or to become boss of the firm and get others to do the colour-matching if one is a painter and decorator.

The undefined careers shown in Table IV are 'blanket' descriptions, where the occupation suggested has many branches, some of which are unsuitable but some perfectly safe for the colour-blind.

The occupations in which the exact task involved needs to be specified are also shown in Table IV. An example is a storeman in a carpet factory who had to hand out wools as required. It was ascertained that these were all numbered, but of course the man who dyed this wool to specification, the man who approved the matching between successive batches, the man who chose them from the colours in the designer's cartoon, and the man who put on the numbers all required accuracy of colour perception. This is the kind of problem which could be answered by a 'Trade Test'—in which the appointee is aslled to perform operations similar to those which he would have to carry out in practice (Wright, 1964).

Two provisos must be made if 'Trade Tests' are adopted (Taylor 1970b):

(1) The conditions must be those encountered in the works—if cables can sometimes be dirty or lighting poor, then must they be so in the test.

(2) The results are not to be regarded as of general application, but only to the trade tested.

An example of this was given by Sloan and Habel (1955), in discussing the requirements for air-crew, which also shows the difference between wide-field and point-source stimulation (stimulating a wide area of the retina or only the fovea).

The last group includes the occupations which are completely ruled out by colour defect (Table III).

Advice to patients

After diagnosing the presence, nature, and extent of the defect, and having ascertained the type of career proposed, what advice should be given? As suggested earlier, this may vary with the stage in that career, so the advice should take cognisance of:

(1) The effect of the defect on schooling;
(2) The effect during the period of training;
(3) The effect on performance in the actual task;
(4) The safety factor—car driving or sailing a boat after dark.

Throughout this consideration, a due sense of humility must be preserved. Except in the careers where any significant error is a bar or the lives of others may be endangered, the frequency of the triumph of determination over difficulties must be remembered.

The fact of the defect should be made clear to the boy and his parents, the problems that it is liable to lead to in his suggested career should be mentioned, and possible alternatives should be suggested or reference made to the careers officer.

Having given all this advice, is any notice whatever taken of it? I began to wonder when I reviewed one of my former patients. This boy, now 17, was found in March, 1968, to have a simple deuteranomaly. At that time his stated career was "teacher of history"—perfectly suitable—however he left school early and was employed as a trainee electrician! This sounded quite unsuitable but on closer questioning it was found that in fact his work was assembling components of switch-gear in a factory, all shining colours of pristine freshness under fully adequate lighting and all parts presented in separate trays to facilitate the operation.

It will have been noted there were only 224 suitable choices of career out of 613 choices made. That is, two out of three colour defective boys choose badly. In 1966 I had already noted that more than half of the choices were unsuitable. I wondered then whether there was something about colour blindness which made the subject gravitate towards the wrong career.

I still wonder.

Summary

In the course of examining 831 Ayrshire school children with deficiency in red-green vision, a decision had to be made as to the suitability of suggested future careers. Recomendations were made concerning future difficulties or dangers, and the basis upon which these suggestions may be made are discussed.

I am indebted to Mr. G. Donald, D.A. Senior Lecturer, Department of Medical Illustration, Glasgow University, for the figures.

I have also to acknowledge the assistance of my colleague Dr. K. Ahmad in 1969 and 1970 with the 100-Hue and pseudo-isochromatic tests.

Appendix

Tests used

1. PSEUDO-ISOCHROMATIC PLATES

Ishihara
Tokyo Medical College
American Optical (H.R.R.)
Farnsworth F2

II. ISOCHROMATIC DISCRIMINATION TEST

Farnsworth's 100-hue Test.

III. ANOMALOSCOPES

Nagel, Model II

Pickford (1966) Model

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Herpes zoster ophthalmicus with trochlear nerve involvement after alcohol injection into the Gasserian ganglion

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Herpes zoster wherein the trigeminal ganglion is affected was first described by Jonathan Hutchinson (1869), but to this day many aspects of the disease are not fully understood. The virus of zoster seems to be identical with varicella virus yet the clinical manifestations differ markedly.

In the past, two types of zoster were thought to exist; idiopathic (epidemic) and symptomatic (secondary) (Duke-Elder, 1965). It is not sufficiently widely appreciated that all zoster is due to reactivation of latent virus. What makes the virus replicate is still often obscure. What are the reactivating factors, and what mechanisms are involved?

In herpes zoster ophthalmicus (HZO), the nerves to the ocular muscles are occasionally involved, the 3rd most commonly, followed by the 6th nerve, the 4th nerve being the rarest (Edgerton, 1945). The factors responsible for such involvement have not been identified with any certainty.

A case is here described of a woman who developed HZO after an alcohol injection into the ipsilateral Gasserian ganglion for "tic douloureux". Subsequently the trochlear nerve on that side became involved.

The purpose of this paper is to suggest the existence of a correlation between these events and thereby to shed some light on the questions posed above.

Case report

A 72-year-old woman came to the Casualty Department complaining of pain over the right side of the face for the previous 5 days. She was mildly febrile and was vomitting.

Past history

She had had severe rheumatoid arthritis for several years and had been taking prednisolone tablets for the past 8 years. At the time of admission she was taking a maintenance dose of 7·5 mg. daily. She had contracted chicken pox at the age of 6 years. In July, 1970, she developed right-sided trigeminal neuralgia (tic douloureux) for which, on October 7, 1970, the Gasserian ganglion was injected with 1 ml. 90 per cent. alcohol.

Examination

The corrected visual acuity was 6/18 right and 6/6 left. Vesicles were present on the right side of the face in the distribution of the ophthalmic division of the right trigeminal nerve, including the naso-ciliary branch. The affected area was anaesthetic and painful (anaesthesia dolorosa). There was a pseudo-ptosis and a mucopurulent conjunctivitis. External ocular movements were full. Corneal sensation was reduced. The intraocular contents were normal. No other cranial nerves were affected at that time.

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Diagnosis

Herpes zoster ophthalmicus was diagnosed and the patient was admitted to hospital.

Investigations

Blood pressure 100/50 mm.Hg; Hb 95 per cent; R.B.C. 4,500,000 per cu.mm; W.B.C. 10,000 per cu· mm; erythrocyte sedimentation rate 4 mm. 1st hr (Westergren). Chest and skull *x* rays were normal· Complement fixation-test for herpes simplex was 1 : 4 and to varicella-zoster 1 : 128.

Treatment and progress

She was treated with dressings of 40 per cent. idoxuridine in a dimethyl-sulphoxide base (DMSO) to the affected area, and chloramphenicol ointment to the eye. She had been taking prednisolone 7·5 mg. for the past 8 years and this dosage was continued during her illness.

Result

She made a good but slow recovery and was discharged after 2 weeks in hospital. After 7 days, however, she complained of diplopia, and examination revealed a right superior oblique paresis (Fig. 1, opposite). A repeat Hess chart 6 weeks later showed a large degree of recovery (Fig. 2, opposite).

Discussion

The clinical manifestations of herpes zoster have been said to arise idiopathically (epidemic) or symptomatically (secondary). The former is now known to be due to infection by a varicella-zoster virus. There is increasing evidence that secondary zoster represents a reactivation of a latent V-Z virus dormant in the tissues, which has acquired neurotrophic propensities (Boyd, 1958; Duke-Elder, 1965; Juel-Jensen, 1970). After varicella infection in childhood, the antibody titre to V-Z virus falls rapidly to 1 : 4 or thereabouts in the post-infective phase, and it remains at this level until middle age. After this time there is a further drop in the antibody level. As a rule shingles is a disease of the over-50s, but the mechanism of this reactivation is not known. Many precipitating factors have been suggested, such as a neoplasm (Moynihan, 1964), infection (Gelfand, 1951), *x*-irradiation (Ellis and Stoll, 1949), physical trauma (*e.g.* corneal foreign body), or emotional trauma (Giroire, Charbonnel, and Vercelleto, 1960; Juel-Jensen, 1970).

The mechanism of involvement of other cranial nerves is speculative. It may be that the infection spreads from the trigeminal nerve to other motor nerves crossing the cavernous sinus (Godtfredsen, 1948; Hermann, 1962). It was suggested by Kendall (1957) that herpes zoster is an affection of the central nervous system and not a radicular or purely dorsal root ganglion affection. This would explain more logically the occasional involvement of motor nerves in the disease. But whatever the mode of spread, such spread would probably be facilitated, or even made general, by the administration of steroids (Merselis, Kaye, and Hook, 1964).

In order to demonstrate that so-called secondary herpes zoster is in fact a reactivation of latent V-Z virus in the tissue it would be necessary to show that:

(*a*) The varicella virus is identical with that of herpes zoster,

(*b*) The patient has been infected by varicella,

(*c*) There had been some precipitating factor,

(*d*) V-Z virus was present in the affected tissue.

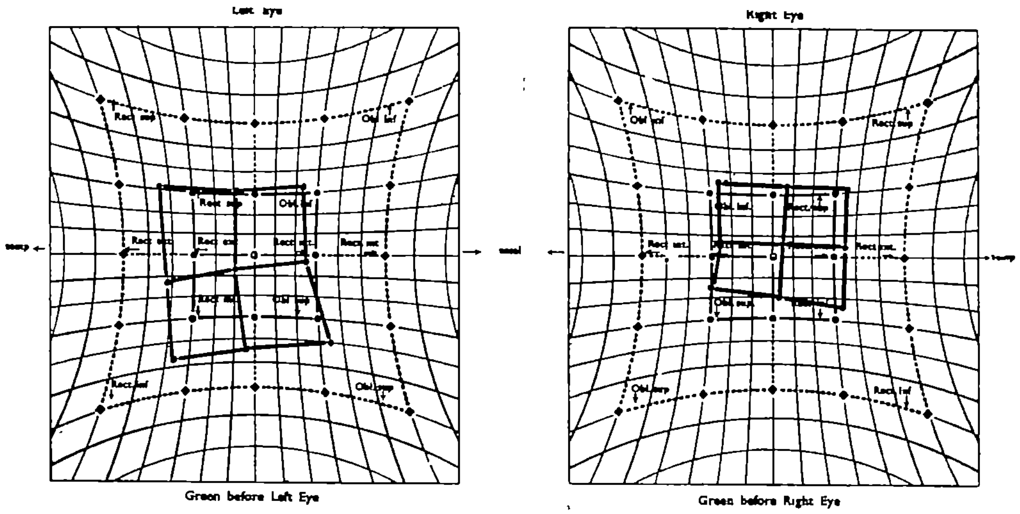

FIG. 1 *Hess chart, showing right superior oblique palsy*

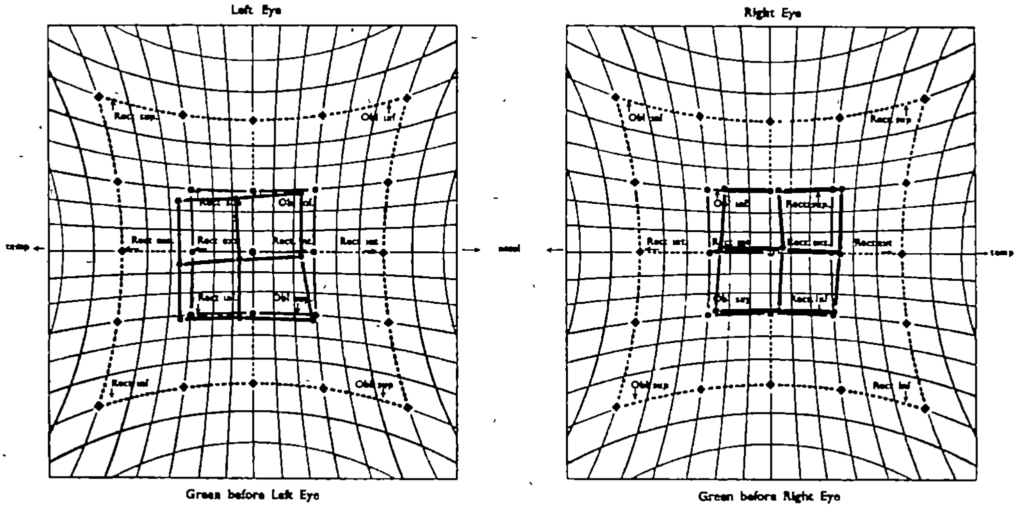

FIG. 2 *Hess chart, showing marked improvement of right superior oblique palsy* 6 *weeks later*

It is generally agreed that the viruses of varicella and zoster are immunologically and morphologically identical. Histologically the cutaneous lesions of chicken pox and shingles are very similar (Thygeson, 1956).

In this context it is interesting to recall that Bruusgaard (1932) inoculated vesicular fluid from cutaneous lesions of a herpes zoster patient into eighteen children, four of whom subsequently developed classical chicken pox and four herpes zoster.

The patient here presented had had varicella as a child. It is suggested that the alcohol injection was the precipitating factor of her zoster. It is true that a lapse of 4 weeks between injury and effect is rather long, but the exact mechanism whereby a provocation could reactivate a latent virus is not known and it could well be that the alcohol took that long to produce injurious fibrosis or necrosis in or near the ganglion.

Juel-Jensen (1970) showed that, of a series of 100 patients with herpes zoster, 65 gave a history suggesting a precipitating event; in 38 per cent. this took the form of trauma to the part affected (Table).

Table *Cause provoking zoster in* 100 *successive patients* (*from Juel-Jensen*, 1970)

Cause	*No. of cases*
Physical trauma	38*
Frontal sinusitis	9
Malignancy	4
Ultraviolet light	3
Diabetes – no injury	3
Chemical	2
Severe emotional upset	2
Rheumatoid arthritis	2
Steroid cream rubbed into area	2
All probable causes	65
No cause discovered	35

*One of these patients also had malignancy, one rheumatoid arthritis.

Evidence that V-Z virus was present in the trigeminal ganglion in the above case is of course not available. However, Tomlinson and Esiri (1971) were able to demonstrate just this in a patient with HZO who subsequently died. In their case the virus was demonstrated in both the peripheral and proximal axons of the trigeminal ganglion as well as in the ganglion itself, but it is admitted that their specimens in no way show whether the virus travelled centripetally from the skin along the axons or centrifugally from the brain stem.

Involvement of ocular motor nerves is very infrequent, though no cranial nerve is exempt. Thus, in a series of 2,250 patients with herpes zoster ophthalmicus, Edgerton (1940) found forty with 6th nerve palsy and only 21 with 4th nerve palsy.

There is evidence to show that a localized herpes zoster may well become generalized under certain conditions. These include the treatment with systemic steroids or ACTH (Merselis and others, 1964), radio-mimetic drugs and *x*-irradiation (Ellis and Stoll, 1949; Hope-Simpson, 1965). It would seem that, if herpes zoster is in fact a disease of the central nervous system as suggested by Kendall (1957), large doses of steroids would facilitate a widespread dissemination of the infection, and small doses might allow a relatively limited spread to affect one, two or a group of cranial nerves.

Conclusion

It is suggested that in this case an alcohol injection into the Gasserian ganglion acted as a precipitator in the reactivation of latent V-Z virus, and that this was facilitated by the fact that the patient was already on systemic steroids and further that this allowed the infection to escape the confines of the trigeminal nerve to spread over and include the trochlear nerve on the same side.

Summary

A patient is presented who had been on long-term systemic steroids and who developed herpes zoster ophthalmicus after an alcohol injection into the Gasserian ganglion. This

patient also developed a paralysis of the trochlear nerve on the same side.

A suggestion is made that these three factors are linked.

My thanks are due to Mr. Philip Awdry for permission to use his case. Dr. Juel-Jensen for kindly allowing me to publish Fig. 3, and to Mrs. MacLellan, chief orthoptist, for the Hess charts.

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Infection of the eye by tapeworm *Coenurus*

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The adult tapeworm of the *Multiceps* variety is quite a common parasite of the bowel of canine animals. In temperate climates it may be found in the domestic dog and the most common intermediate hosts are the sheep ('gid') and the rabbit. In Africa the natural cycle of the worm is not fully known, but it seems likely that the adult is found in such animals as the jackal and the intermediate host may be the porcupine or swamp rat (Nelson, Pester, and Rickman, 1965) or smaller rodents (Fain, 1956). Man has been infected by the *Coenurus* stage of this tapeworm in fifty cases (Templeton, 1968), in eight of which the eye was affected (Boase, 1956; Epstein, Procter, and Heinz, 1959; Raper and Dockeray, 1956; Templeton, 1968; Vanderick, Fain, Langi, and van Balen, 1964; and Wainwright, 1957). We here report five new cases of ocular disease caused by this parasite and review experience of this unusual problem.

Case reports

Brief details of our cases and those previously recorded are shown in the Table. The vitreous, the orbit, and the subconjunctival tissue have been involved, but localization in

Table *Details of thirteen recorded cases of* Coenurus *infection of the eye and orbit*

Case	*Age (yrs)*	*Sex*	*Site*	*History*	*Tribe*	*Country*
Present series 1	14	F	Anterior chamber	Few days	Lugbara	Uganda
2	1	M	Subconjunctival	6 mths	Kiga	Uganda
3	1	F	Subconjunctival	?	Toro	Uganda
4	Adult	M	Vitreous	3 yrs	Nkole	Uganda
5	35	M	Vitreous	Long time	Kiga	Uganda
Templeton (1968)						
(Case 14)	35	F	Vitreous	?	Lugbara	Uganda
(Case 12)	2	M	Subconjunctival	1 yr	Nyoro	Uganda
Boase (1956)						
(Case 2)	1	F	Subconjunctival	3 wks	Ruanda	Ruanda
(Case 1)	21	M	Vitreous	1 wk	Nkole	Uganda
Wainwright (1957)	51	M	Vitreous	3 mths	?	S. Africa
Epstein and others (1959)	3½	F	Vitreous	?	White	S. Africa
Raper and Dockeray (1956) (Case 3)	12	M	Rectus lateralis muscle	?	?	Kenya
Vanderick and others (1964)	6	F	Subconjunctival	?	Hutu	Ruanda

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the anterior chamber appears to be unique to our Case 1 and for this reason further details are given below recorded.

An adolescent African girl of the Lugbara tribe presented with a history of pain in the eye for a few days.

Examination

There was injection of the globe for which antibiotic was instilled. The cornea, anterior chamber, pupil, and media were noted to be normal. She returned 9 days later with a pronounced ciliary flush and hypopyon. Despite the addition of atropine, her condition worsened and the lower half of the cornea became generally infiltrated. On the 17th day after she was first seen, a round foreign body was observed in the anterior chamber behind the infiltration and keratic precipitates. After a further 3 days its size had increased and careful observation with the corneal microscope showed peristalsis in the cyst-like body (Fig. 1).

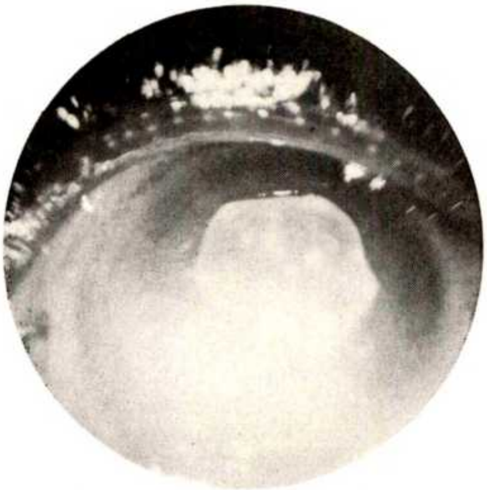

FIG. 1 *Anterior chamber, showing* Coenurus in situ (*Case* 1)

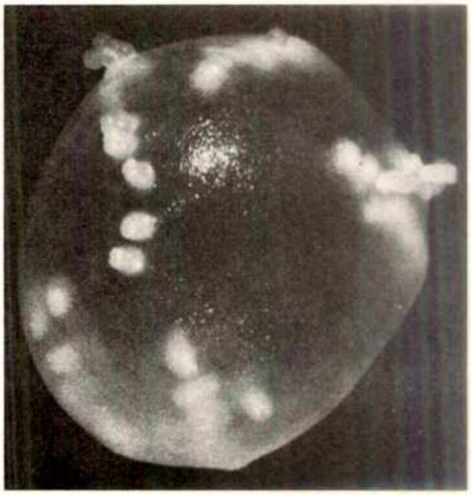

FIG. 2 Coenurus *cyst from Case* 2, *showing scolices projecting from surface.* ×12 (*Courtesy of Prof. Paul C. Beaver*)

Treatment and Result

The cyst was removed intact by surgery. The eye healed slowly, and a year later showed vitreous bands extending to the corneal incision and cholesterol crystals in the posterior chamber.

The cyst measured 4 mm. in diameter and bore sixty developing scolices which appeared to be arranged in eight rows of three to ten scolices each row. They radiated from a pole of the *Coenurus* and were restricted to one hemisphere (Fig. 2, overleaf.) None of the scolices were developed sufficiently to bear suckers.

Discussion

Infection of man by *Coenurus* in temperate regions of the world usually results in central nervous system involvement in adult patients. Thus, of the eighteen cases reported from locations outside tropical countries, thirteen were located in the brain or spinal cord and usually affected adults. In tropical Africa 26 out of 32 recorded cases have presented with a subcutaneous *Coenurus*. Most of the patients with subcutaneous disease are children and the commonest site of involvement is the trunk. These striking differences argue that the mode of infection and possibly the species of parasite is different in the two areas. Unfortunately little information is available on this subject in spite of various feeding experiments. Attempts have been made to classify the species on the basis of the arrangement of the scolices in the *Coenurus* but these are very unsatisfactory. Thus Brumpt (1936) delineated the species *M. seriales* largely on the basis of the linear arrangement of scolices in the *Coenurus*.

All five cases in which the cyst was located in the subconjunctival region occurred in children. All lived in the mountains which form the eastern wall of the Western Rift Valley at the border between Congo and Uganda. As such they show striking similarities to the Ugandan patients with subcutaneous disease who are often of a similar age and reside in the same part of the country. It is possible in view of the age of the patients that such cases result from inoculation of the larva directly into the conjunctiva or skin during early toddler life when the trunk and eyes are frequently close to the ground which may be contaminated. Removal of the cyst (Fig. 3) is seldom difficult and results in a complete cure.

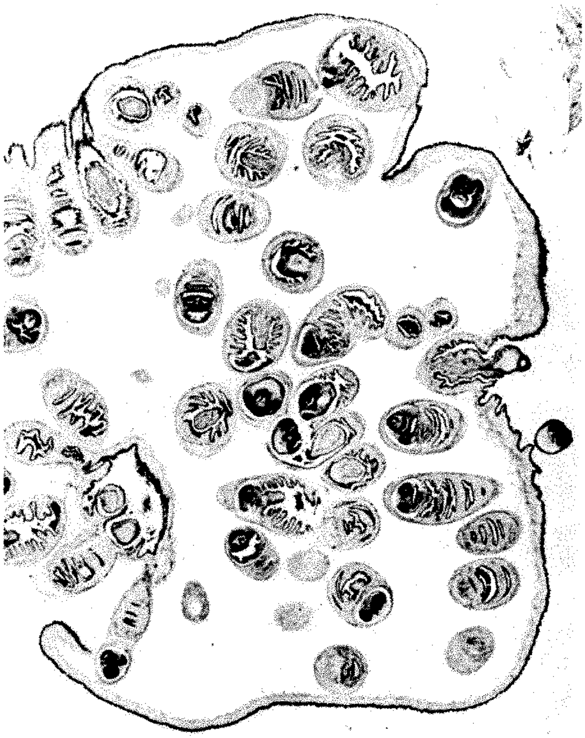

FIG. 3 *Photomicrograph of* Coenurus *from Case* 3, *showing numerous scolices.* ×35

In all but one case (the only white patient recorded, a girl aged 3½ years: Epstein and others, 1959), involvement of the interior of the eye occurred in older patients and as such more closely resembled the cases of central nervous system involvement seen in temperate climates. A more likely route of infection in such cases appears to be the mouth, with spread to involve the eye or central nervous system perhaps *via* the blood stream. In the early stages of infection the cyst provokes little or no reaction and if it is removed at this stage useful vision may be preserved. However, as the cyst matures, it excites an inflammatory reaction and the eye becomes painful, glaucomatous, and finally blind.

In the late stages of infection all that remain are the teeth and suckers of the scolices surrounded by inflammatory tissue in which calcium and even bone may be found. Infection of the eye by this parasite is almost certainly more common in Uganda than the paucity of reports would indicate. In the late stages of infection identification is impossible and many patients do not present at hospital until panophthalmitis is too far advanced to be certain of the mode of onset.

The exact identification of *Coenuri* is difficult and in fact the taxonomic position of the whole *Multiceps* family is under some dispute. Some favour generic status for this group whereas others regard it as a species within the genus *Taenia*. Whichever classification is eventually adopted, all the cases seen in Uganda conform to a type and most closely resemble the species named *brauni* (Setti). Fain (1956) and Nelson and others (1965) favoured this identification for the *Coenuri* which were found in animals in Ruanda and Kenya respectively. Cases involving the central nervous system have usually been diagnosed as *M. multiceps* and are frequently multilocular, whereas ocular cases are usually uniocular (except Boase, 1956, Case 1). *Coenurus cerebralis* is usually assumed to have been due to accidental involvement in the natural dog-to-sheep life cycle. In tropical Africa no case of involvement of the central nervous system has been recorded in humans and no well-documented infection in sheep has been found (Nelson and others, 1965). It thus seems that the cerebral and subcutaneous forms of infection are due to differences in the species and life cycle of the parasite. Ocular cases have been seen in both temperate and tropical Africa and it would be of great interest to compare the morphology of cases involving the vitreous in Uganda and South Africa to see if there are morphological differences in the *Coenuri* in the two areas.

Summary

Five new cases of ocular involvement by *Coenuri* of the *Multiceps* species are recorded. Subconjunctival infection is seen in young children and may be a result of direct inoculation with infected material. Involvement of the globe occurs in older people and is possibly due to spread from the bloodstream. In the early stages the *Coenurus* appears not to cause irritation and may be removed without gross damage to the eye. Later in its development reaction with fibrosis and blindness is the general rule.

Our thanks are due to Dr. Dale E. Wykoff of the Walter Reed Army Institute of Research, and Prof. Paul C. Beaver of Tulane University, who kindly confirmed our diagnoses in some of these cases and supplied two of the photographs.

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Hyaloideocapsular ligament of Wieger and vitreous loss in the course of intracapsular lens extraction

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With modern surgery the incidence of vitreous loss should not be higher than 3 per cent. (Vail, 1955; Müller, 1966; Kettesy, 1967). The surgeon fears vitreous loss because it may give rise to such complications as astigmatism, secondary glaucoma, drawn-up pupil, retinal detachment, bullous keratopathy, corneal opacities, oedema of the optic disc and macula, or iridocyclitis which may progress to shrinkage of the globe. Statistics show that approximately 6 per cent. of such eyes are lost within a year and usually within 2 months. Of the remainder, 18 per cent. have no useful vision after a year and only 20 per cent. have vision better than 6/18 after 3 years; after 3 years, however, the chances of retaining this vision are high (Vail, 1965).

Present investigations

To discover the cause of vitreous loss after the use of modern preoperative measures and modern surgery, 200 intracapsular lens extractions for immature and mature cataracts were reviewed.

Methods

Preoperatively several precautionary measures were taken to prevent loss of vitreous during the operation:

(1) There was no straining as in coughing.

(2) The instruments were of the best type.

(3) There was no pressure on the globe.

(4) Anaesthesia, including facial akinesia, was perfect.

(5) A retrobulbar injection was given for extraocular muscle paralysis.

(6) Hypotensive agents such as acetazolamide were used before operation, with hypotensive osmotic therapy such as oral glycerine, and a purgative, combined with digital pressure on the globe (Atkinson, 1955).

(7) Use of a Flieringa-Bonaccolto ring if there was a tendency to scleral collapse.

(8) The use of analgesics, hypnotics, tranquilizers, sedatives, and antihistaminics up to the level of toleration in each patient to induce calm and prevent engorgement of the uveal vessels, especially choroidal vessels.

Technique

Lens extraction was performed by the multiple methods technique (Mortada, 1963, 1965).

A von Graefe knife section was made at the corneal side of the limbus with a very small conjunctival

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flap, cutting up from 1 mm. above the horizontal corneal meridian on either side. A key-hole iridectomy was performed, and three conjunctivo-corneosclero-conjunctival virgin silk sutures were placed at the 10, 12, and 2 o'clock meridians but not tied. The extraction began by external pressure zonulotomy (not that used by Smith, 1926). Pressure was applied with the tip of the strabismus hook moved on the sclera along the lower 180° arc, 2 to 3 mm. from the limbus without counter pressure. The aim of this pressure was to make a small scleral identation, giving a shelf aiming at raising the lower pole of the lens, thus separating the lower zonular fibres and lower part of the hyalocapsular ligament and subluxating the lens from below.

Inspite of this special lower external pressure aimed at tumbling the lens, the lens subluxated from below in 35 per cent. of cases. In 60 per cent. the lens presented in the wound with its upper pole first and in 5 per cent. it appeared to be reluctant to leave the eye after 3 minutes of lower external pressure.

Once the lens was subluxated the lens capsule was held by the non-toothed capsule-forceps just anterior to the equator from side of the subluxated lens. In cases of lower subluxation the extraction was continued by tumbling (Arruga, 1933). If the lens subluxated from above or had no tendency to leave the eye, the extraction was continued by the head-first technique described by Kirby (1938).

The operation was concluded by tying the three corneoscleral sutures, reposition of iris pillars, air injection into the anterior chamber, and reposition of the conjunctival flap.

Results

(A) In 35 per cent. of cases in which the lens subluxated firstly from below and extraction was by tumbling, there was no vitreous loss.

(B) In 60 per cent. of cases in which the lens subluxated firstly from above and extraction was by the upper pole first delivery technique, there were four cases of vitreous loss.

(*i*) As the lens was raised from above, in six cases the hyaloid separated from its attachment to the ora serrata in the upper part of the globe and the vitreous bulged out between the lens and the scleral lip of the wound. In four cases the vitreous was replaced by the back of the lens and in two other cases, as delivery continued and because of the adherent hyalocapsular attachment, the exposed bulging vitreous face ruptured causing vitreous loss.

(*ii*) As the lens was raised from above, in two cases of myopic eyes, the anterior hyaloid face was found to be degenerated with fluid vitreous seeping out during the extraction.

(C) In 5 per cent. of cases where the lens showed no inclination to leave the eye, the extraction was continued by the upper pole first delivery technique, and because of the adherent hyalocapsular ligament in four cases, the hyaloid membrane was partly detached with the adherent posterior lens capsule, which led to vitreous loss.

It is known that neither alpha-chymotrypsin nor cryoextraction has any effect on the ease of separation of the hyalocapsular ligament.

Discussion

To know the degree of attachment of the hyaloid membrane to the ora serrata, posterior lens capsule, and zonule is of great importance during intracapsular lens extraction.

The hyaloid membrane, the condensation of the vitreous face (Duke-Elder, 1930; Hilding, 1954), is firmly attached in a ring 2 to 3 mm. wide which extends forwards from the ora serrata to the pars plana of the ciliary body.

The vitreous adheres to the posterior surface of the lens by the hyalocapsular ligament (Wieger, 1883), which forms a ring 8 to 9 mm. in diameter 1 mm. from the periphery of the lens. Elsewhere in the patellar fossa, the vitreous is separated from the lens by the capillary space of Berger (1883), which sometimes contains aqueous (Duke-Elder and Wybar, 1961). In the course of intracapsular extraction the ligament slowly peels away from the patellar fossa stage by stage (Vail, 1937). An adhesion of the hyaloid layer of the vitreous to the capsule of the lens, which is usually associated with a persistent hyaloid artery, a condition relatively common in early life, may result in serious vitreous loss during an intracapsular extraction (Vail, 1954; Wolter, 1961).

Some zonular fibres of Zinn may be firmly and intimately associated with the vitreous at their point of origin, and this is important if the vitreous is disturbed by the intracapsular method of lens extraction (Vail, 1952). This attachment has been called the hyalozonular ligament (Minsky. 1942).

Summary

(1) With modern preoperative precautions and operative techniques vitreous loss occurred in 4 per cent. of 200 intracapsular lens extractions for senile cataract.

(2) The main cause of vitreous loss was the effort required to separate a closely adherent hyalocapsular ligament.

(3) Neither alpha-chymotrypsin (Barraquer, 1958) nor the cryo probe (Krwawicz, 1961) makes the separation of the hyalocapsular ligament any easier or safer.

(4) In the multiple methods technique of cataract extraction (*i.e.* using tumbling or upper pole first extraction according to the site of lens subluxation noted after using a specially designed method of external pressure for mechanical zonulotomy (Mortada, 1963, 1965), the hyalocapsular ligament is slowly peeled away stage by stage, thus minimizing the risk of vitreous loss.

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Benign epithelioma of the iris

A clinico-pathological case report

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Neoplasms of the pigmented epithelium of the eye are rare, those of the iris epithelium being especially unusual. Reviews by Ashton (1964) and Duke-Elder and Perkins (1966) present benign epitheliomas of the iris as black masses arising from the epithelium and pushing forwards into the stroma. The present case is completely different in nature, and appears to be the first of its kind reported.

Case report

A farmer aged 50 years vaguely noted a change in the vision of his right eye for several months. In March, 1969, he attended an optometrist who found a lesion in the right iris. No abnormality had been noted by the same optometrist during an examination 5 years previously. The patient was sent to Melbourne for ophthalmological management.

Examination (March 24, 1969 : R.F.L.)

Both eyes were free of inflammation and the irides were of the blue type with scattered honey-coloured freckles.

The right eye showed a pale yellow spherical mass approximately 2 mm. in diameter within the iris stroma almost midway between the pupil margin and the root of the riris in the upper temporal sector (Fig. 1). Large curly new vessels coursed in the iris stroma from the periphery radially to,

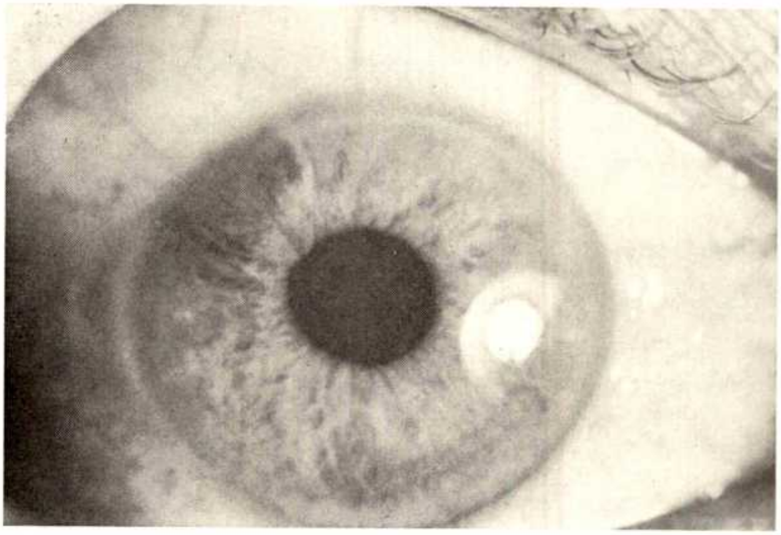

FIG. 1 *Pale, heavily vascularized, benign epithelioma of the iris*

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around, and over the tumour extending to the pupil margin while, deep in the stroma and almost obscured by it, other vessels could be seen in the 12 o'clock position slightly away from the tumour.

The pupil margin was drawn slightly towards the tumour, there was no ectropion of the pigment epithelium and the pupil reactions were very little affected. The involved segment of the iris appeared to be lifted away from the lens which could be seen to have anterior opacities in this area. The visual acuity in each eye was 6/9.

Management

The tumour was causing lens opacities and as it did not involve the periphery of the iris, excision was advised rather than observation. The tumour presented such unusual features in its duration and appearance that no presumptive diagnosis could be given, but leiomyoma of the iris was thought to be probable. Some apprehension was felt for difficult haemorrhage from the numerous aberrant vessels.

The tumour was excised by sector iridectomy, after radial cuts on each side. No undue bleeding occurred at the time. On lifting the iris, a smooth, avascular, cream, globular tumour was seen to protrude from the pigment epithelium and a circular small crater in the anterior lens surface was seen at the site previously occupied by the tumour.

Three days postoperatively a moderate hyphaema showed as clotted blood over most of the iris, but this cleared in 5 days and progress was otherwise uneventful. In the sector iridectomy the lens showed irregular, anterior, radial opacities as well as the small crater noted above.

Result

One year postoperatively the visual acuity in the right eye was 6/6 with + 0·5 D sph., + 1·5 D cyl., axis 30°. A year later the vision was the same and the lens opacities were unchanged.

Pathology report (C.H.G.)

Microscopic appearances

Sections showed a lentil-shaped growth measuring 2 mm. in diameter by 1 mm. in thickness situated on the posterior surface of the iris midway between the extremities of the excised tissue. The growth was covered anteriorly by the iris and posteriorly by an incomplete layer of pigmented iris epithelium. The iris stroma contained large thin-walled supernumerary vessels devoid of the wide adventitial sheaths characteristic of normal iris vessels.

The tumour consisted of fusiform, cuboidal, and polygonal epithelial cells which appeared to have originated from the iris pigment epithelium round the perimeter of the growth (Fig. 2, opposite). A minority of the tumour cells contained melanin granules. In the centre of the growth the tumour cells were compressed into thin strands to form a network. The interstices of this net were filled with eosinophilic stroma in which small endothelial-lined channels containing red blood cells could be discerned. These vessels were probably branches of the large vessels in the iris.

The stroma varied in appearance, being faintly fibrillated and vacuolated in some areas while in others it was structureless and hyalinized. In the centre of the growth the stroma had undergone granular calcification and in the immediate vicinity of the granules there was a small amount of mucoid substance (Fig. 3, opposite). The appearance of this stroma and its relationship to the epithelial cells of the tumour suggested that it was a product of these cells and perhaps an excessive formation of basement membrane substance.

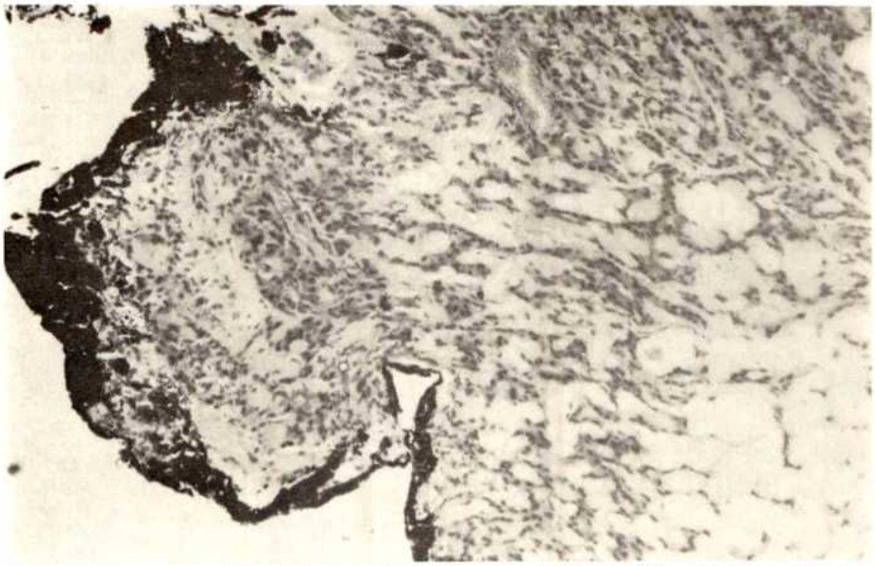

FIG. 2 *Appearance of growth by hyperplastic pigment epithelium. Haematoxylin and eosin.* ×75

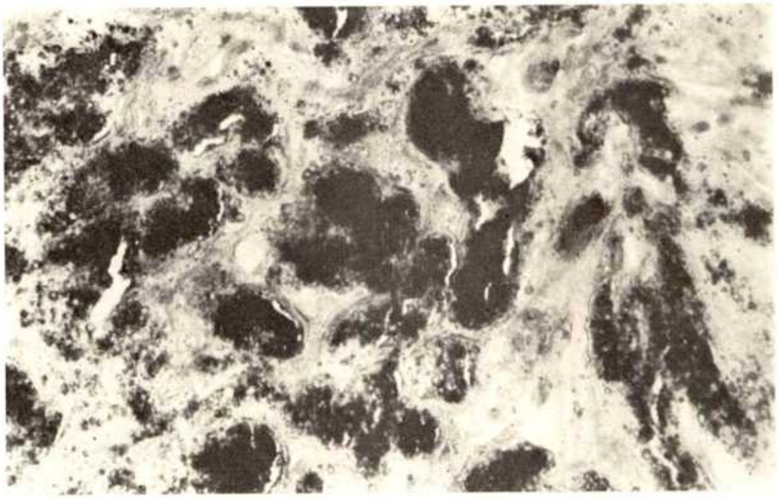

FIG. 3 *Granular stromal calcification in centre of tumour. Von Kossas stain.* ×170

Discussion

This benign epithelioma of the iris pigment layer is different from previously reported black tumours of the iris epithelium. Macroscopically it was pale yellow and microscopically the pigment cells were collected mainly around the periphery. In the centre of the tumour the pigment cells appeared to have taken on another function in forming an eosinophilic stroma with the excitation of a very vascular reaction.

Ashton (1964) showed the interrelationships between pigment epithelium and smooth muscle cells which both arise from the pigment layer of the neuroepithelium; and how tumours may arise containing cells showing not only the distinct features of these two cell types but also intermediate cells with features in common, thus making cell classification difficult.

The pigment layer of the neuroepithelium has other potentialities, namely, the formation of basement membrane. This is best seen with retinal pigment epithelium, whereas this function is not developed in iris epithelium. However, in tumour formation, some cells may manifest suppressed potentials and this benign epithelioma of the iris may have done so. The calcification may represent degeneration in an abnormally produced basement membrane substance.

Its appearances together with its unusual posteriorly directed growth are perhaps significant in indicating deeply ingrained features of the posterior neuroepithelium in contrast to the myoepithelial-pigment cell features of the leiomyomas which favour the anterior layer of the neuroepithelium.

Summary

A cream-coloured, rapidly growing vascularized tumour of the iris was excised and found on microscopy to be an unusual benign epithelioma of the iris. Propositions are submitted to suggest that this tumour has a different pathogenesis from the usual (but rare) pigmented benign epitheliomas of the iris and leiomyomas.

We wish to thank Dr. J. Paul Borger for referring this case and for his skilled assistance in management.

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Central retinal vein occlusion complicating iron deficiency anaemia

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Sudden blindness as a consequence of severe blood loss was well known at the turn of the century, when a common cause of blindness in young people was anaemia due to blood loss from the gastrointestinal tract or to abortion (Gowers, 1904). The retinal changes described include pallor of the disc, sometimes with disc oedema, and small numbers of retinal haemorrhages and exudates. Such retinal abnormalities usually develop within 48 hours of haemorrhages and occur typically in patients rendered anaemic by repeated episodes of blood loss rather than a single major haemorrhage. Transient impairment of retinal blood flow during episodes of hypotension was considered to be the most likely cause of the ocular changes in such cases by Pears and Pickering (1960). Though retinal haemorrhages and exudates often occur in severe chronic iron deficiency anaemia (Holt and Gordon-Smith, 1969), the retinal abnormalities are not usually severe and consist, in the main, of "cotton wool" exudates. Profound retinal damage suggesting central retinal vein occlusion would appear to be a most unusual complication of iron deficiency anaemia; such a case is reported here and the pathogenesis of the retinal changes is discussed.

Case report

A 44-year-old married woman (RI 476584) was admitted to hospital complaining of blurred vision in the left eye of 10 days duration. Apart from shortness of breath on exertion and a tendency to bruise easily, she had no other symptoms.

PHYSICAL EXAMINATION

She was strikingly pale with a few bruises on the right thigh and the feet. There was an aortic ejection murmur radiating into the neck. The brachial blood pressure was 120/70 in each arm. The remainder of the examination gave normal results.

OPHTHALMIC EXAMINATION

The visual acuity was 6/5 in the right eye and 6/18 in the left. The intraocular pressures were 14 mm.Hg in the right eye and 13 mm.Hg in the left measured by applanation tonometry. The right fundus was normal but the left fundus showed florid features of central retinal vein occlusion with blurring of the disc margin, venous engorgement, haemorrhages, soft exudates, and macular oedema (Fig. 1, overleaf). Ophthalmodynamometry showed the pressure to be 100/45 on each side.

INVESTIGATIONS

Hb6·2 g./100 ml.; mean corpuscular haemoglobin concentration 30 per cent; reticulocytes 3 per cent.; platelets 280,000/cu. mm.; white blood cells 4,800/cu.mm. (normal differential); blood film—marked hypochromia, anisocytosis, and poikilocytosis; erythrocyte sedimentation rate 4 mm. 1st hr.

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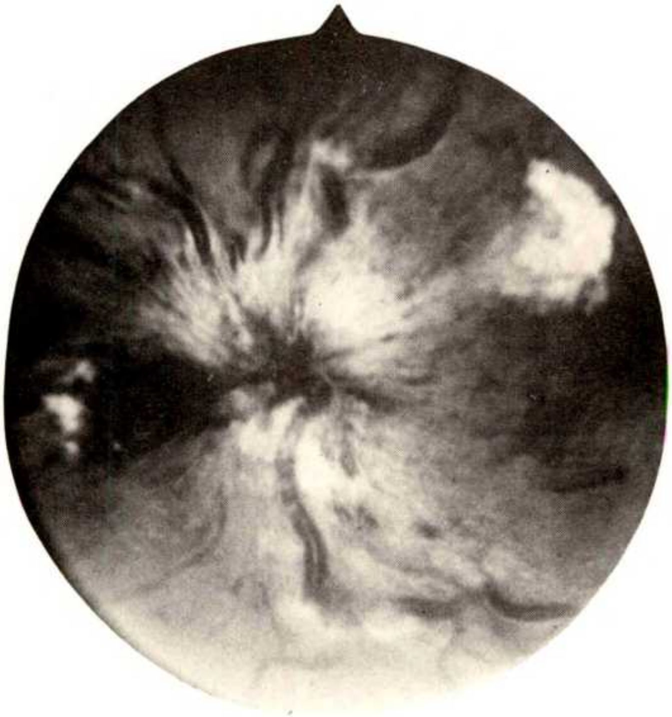

FIGURE *Left fundus, showing features of retinal occlusion*

Serum iron 30 μg./100 ml.; serum folate 3 ng./ml. One stage prothrombin time, kaolin cephalin time, normal. Fibrinogen titre normal.

Bone marrow Very cellular, showing active normoblastic erythropoiesis but no stainable iron.

Plasma urea, electrolytes, calcium, phosphate, cholesterol, uric acid, proteins and albumin, alkaline phosphatase, bilirubin, lactic dehydrogenase, glutamic oxaloacetic transaminase levels all normal. Antinuclear factor—negative.

Urine Normal; no haemosiderin.

Repeated faecal tests for occult blood were negative.

Jejunal biopsy Normal histology.

Ferrous iron absorption 21 per cent. (normally 30 per cent. in iron deficiency).

Gastrin test meal Achlorhydria with low intrinsic factor secretion. Intravenous glucose tolerance test—$K_G = 1{\cdot}2$, repeated 6 months later, $K_G = 1{\cdot}1$ (low normal result).

Radiological examination Oesophagus, stomach, small and large bowels normal.

TREATMENT

The patient was transfused with 2 units of packed cells and this was followed by treatment with oral iron.

RESULT

Subsequently no cause for the profound iron deficiency anaemia was discovered and 3 months later the haematological state was normal apart from slight hypochromia of the red cells (Hb 13.3 g./

100 ml.; mean corpuscular haemoglobin concentration 33 per cent.; reticulocytes 0·3 per cent.). At this time the appearance of the left fundus had returned to normal and the visual acuity had improved to 6/5.

She now acknowledged that she had not been so well for many years and had been easily fatigued since the birth of her second child.

COMMENT

Though no previous measurements of her haemoglobin concentration had been made, it seems likely that the iron deficiency anaemia was of long duration, probably related to childbirth. Its perpetuation was most likely to be due to defective absorption of food iron related to gastric achlorhydria, although the possibility of chronic repeated blood loss from the gastrointestinal tract cannot be overlooked, despite the fact that all investigations were negative.

Discussion

The haemodynamic circumstances of the ocular circulation are unique in that the terminal branches of the vascular supply to the eye pass from an extraocular low pressure system into an intraocular high pressure system. Thus the relative perfusion pressure in the retinal vascular system is low compared with the extraocular circulatory system. Factors which disturb this critical perfusion gradient may be responsible for the development of central vein occlusion. Much evidence incriminating arterial circulatory changes in the pathogenesis of the retinal vein occlusion has been found clinically in ophthalmodynamometric studies by Paton, Rubinstein, and Smith (1964) and experimentally by Hayreh (1965). Lowered retinal perfusion pressure leading to a fundus picture similar to that of central venous occlusion has been recognized in carotid insufficiency and aortic arch syndromes (Hedges, 1964) because of the reduced arterial pressure and in cases of carotid-cavernous fistula where the venous pressure is elevated while the arterial pressure is reduced (Sanders and Hoyt, 1969). Central vein occlusion is often a presenting sign of chronic simple glaucoma, the elevated venous pressure secondary to the raised intraocular pressure being responsible for a lowered retinal prefusion gradient.

Whatever the cause of the reduced retinal perfusion gradient, the ensuing hypoxia produces metabolic dysfunction of the capillary and venous endothelium. The veins become distended and leakage of blood occurs through the vessel wall. In our patient the intraocular pressures were normal, there was no clinical evidence of arterial disease, and such findings would have been unusual in a female patient under 45 years of age. We suggest that, despite an apparently adequate perfusion pressure, the quality of the perfusing blood must also be considered and that in our patient the relative anaemic hypoxia caused the development of the venous changes. This hypothesis is strengthened by the return to normality of the retina and visual acuity on correction of the anaemia. The prompt correction of the anaemia by improving the retinal circulation allowed rapid recovery of the macular oedema before degenerative cystoid maculopathy appeared.

Summary

Central retinal vein occlusion developed as a consequence of profound anaemia in a 44-year-old woman. Venous endothelial incompetence as a result of anaemic hypoxia is believed to be responsible for the retinal changes despite the presence of an adequate retinal perfusion pressure.

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Unusual presentation of necrotic nodular scleritis

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Holthouse (1893) described painful ulceration in an apparent nodule of episcleritis, with resulting perforation of the globe (Duke-Elder, 1938). According to Francois (1951), the case reported was not one of episcleritis but the represented first description of necrotic nodular scleritis. Watson (1966) states that the sclera is rarely involved in episcleritis.

All forms of necrotizing scleritis are grouped under the term necrogranulomatous scleritis (Sevel, 1965). Pain is an inconstant feature, being absent in scleromalacia perforans and present in rheumatic nodule (Ashton and Hobbs, 1952) and necrotic nodular scleritis (Franceshcetti and Bischler, 1950). The following case report records painless scleral necrosis, initially presenting as a nodule of episcleritis, and its subsequent treatment by surgery.

Case report

A man aged 44 years attended the out-patients department at the Victoria Hospital, Burnley, on March 9, 1971, complaining of deterioration of vision in the right eye for 3 months. He volunteered the information that a painless swelling on the temporal side of the limbus, which was increasing in size, had been present for 12 months. Since December, 1950, repeated attacks of iridocyclitis had occurred in the right eye. Arthralgia in both knee joints was diagnosed in 1960 when a latex-fixation test was positive.

EXAMINATION

The visual acuity was 3/60 in the right eye and 6/6 in the left. At 7 o'clock in the right eye there was a bright red swelling about 4 mm. in diameter and 2 mm. from the limbus. Corneal sensation was present. The slit lamp showed, superficial to the swelling, slight dilatation of the vessels in the subconjunctival plexus and gross dilatation of the anastomotic superficial episcleral plexus vessels. Seclusio pupillae and cataract were observed but no flare, cells, or keratic precipitates in the anterior chamber.

TREATMENT

Prednisolone drops 8-hrly.

PROGRESS

On March 19, the swelling was a smooth, trilobed, cream-coloured excrescence, about 5 mm. in diameter encroaching on the limbus (Fig. 1, overleaf).

In-patient treatment was advised but the patient refused to enter hospital until April 14. Prednisolone drops were stopped and chloramphenicol ointment was prescribed.

OPERATION

On April 14 the conjunctiva was incised; arising from the sclera was a tumour, which, when punctured, discharged a milky fluid. After excision of the swelling the scleral gap was covered by conjunctiva.

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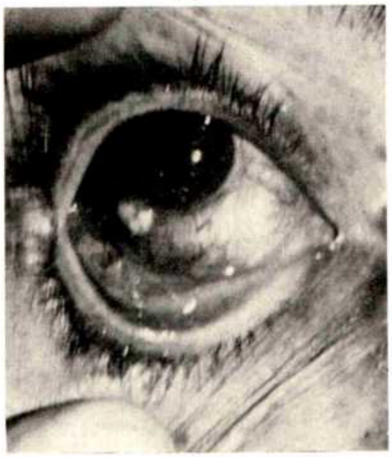
(1)



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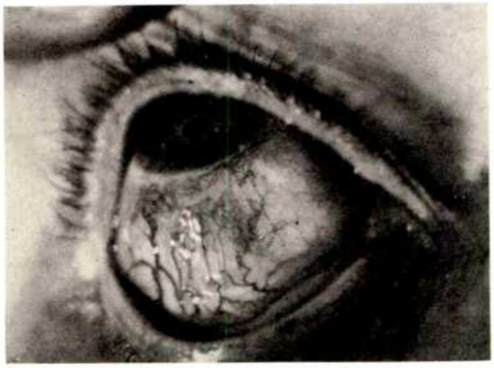

FIG. 2 *Appearance on May* 14, 1971

FIG. 1 *Appearance on March* 19, 1971

PATHOLOGY REPORTS

Fluid. Amorphous necrotic debris. No polymorphs or organisms seen. Cultures sterile. Granulation tissue found on section.

RESULT

On May 14, the sclera had completely healed (Fig. 2).

Discussion

The distinction between episcleritis and scleritis may be difficult. The initial lesion was diagnosed as a nodule of episcleral inflammation. This diagnosis was based on the characteristic appearance of the vascular pattern of the anterior segment of the eye (Watson, 1966). Topical steriod treatment failed to suppress the inflammatory reaction and to prevent necrosis. Considering the chronicity of the lesion, and the juxtaposition in time of local steroid treatment to necrosis, it is surmised that the ncerosis may have been precipitated by the use of prednisolone drops. Excision of the necrotic area may appear to be the best form of treatment. New collagen material has been rapidly laid down with no clinical evidence of scleral thinning or subsequent likelihood of scleral ectasia and staphyloma formation.

Secondary scleritis may complicate uveitis (Duke-Elder, 1938). In this case these are considered to have occurred coincidentally, but with a possible single background, *i.e.* polyarthritis.

The absence of severe pain is puzzling. Possible explanations include toxic involvement of the long and short ciliary nerves by episodes of iridocyclitis causing local damage to the nerves; rapid local involvement of the ciliary fibres in the necrotic reaction; individual raised pain threshold or stoicism.

The differential diagnosis in this case must include scleromalacia perforans which can appear as raised, multiple yellow nodules. It was excluded because the patient was under 50 years old, there was no deforming rheumatic polyarthritis, and the characteristic ocular features were absent (François, 1951).

Summary

A case of painless necrotic nodular scleritis, preceded by episcleritis, is described. Surgical treatment was successful. Differential diagnosis and absence of pain are discussed.

I wish to thank Dr. Behr and Mr. Taylor for the photographs and Mrs. M. J. Hudson for her help in the preparation of this paper.

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The upper fornix trap

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A recent unusual incident made me decide to report two cases that illustrate the importance of a careful examination of the upper fornix in patients complaining of foreign bodies in the eye.

The first patient was a 38-year-old man who had been wearing contact lenses without any complications for over 8 years. The day before he came to see me, he had rubbed his left eye and suddenly discovered that his contact lens had disappeared. He was sure that it had not dropped out of the eye, but, on the other hand, he was unable to find it anywhere in the conjunctiva sac. He had persistent mild foreign body sensation which was still present the next morning. He went to the optometrist who had fitted him, and he in turn referred him to my office since he could not find the lens in the eye either. When I examined the patient, the left eye appeared perfectly calm and on extreme downward gaze with the upper lid elevated, there was no evidence of the lower border of the lens as one usually sees it. Nothing unusual could be palpated through the upper lid. Although I had decided that the patient must have pushed the lens out of the eye when he rubbed it, I was suspicious enough to put a drop on Pontocaine in the conjunctiva and evert the upper lid. Still no evidence of a foreign body. With the help of a flattened rounded glass rod, I swept up into the upper fornix and felt a hard resistance on the nasal side. In lifting the upper tarsal border with the glass rod, I could now see the lower border of the contact lens. To my surprise, the lens had lodged with its concave surface forward in the fornix (Fig. 1). Its lower border was firmly embedded in the soft tissue just above the upper tarsal border and had therefore remained out of view on downward gaze. The lens was easily removed from this trap with the glass rod. I assume that, had the lens been left in this unusual location, it might well have penetrated by pressure necrosis into the

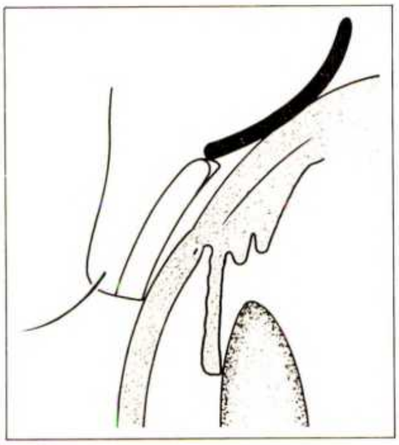

FIG. 1 *Inverted contact lens in upper fornix with its lower border wedged into upper tarsal edge*

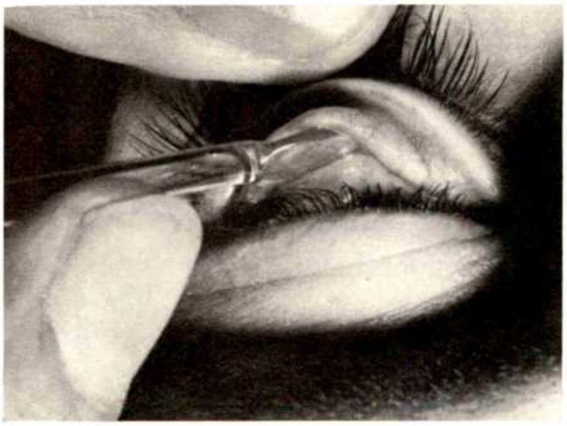

FIG. 2 *Upper fornix visualized by means of a flattened glass rod after eversion of the upper lid*

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upper lid, an occurrence that has been reported in the literature (Green, 1963; Long, 1963; Michaels and Zugsmith, 1963).

The second case is that of a woman whom I saw over 15 years ago. She had been complaining to her ophthalmologist of a foreign body sensation in the right eye for over 2 months. It had started the day after she had cleaned a bird cage. No foreign body had ever been found and all medication had been without avail. The eye again showed no evidence of inflammation and no foreign body was found on double eversion of the upper lid. However, after instilling Pontocaine and lifting the upper border of the everted upper tarsus with a flat glass rod under good illumination (Finoff), I could see a millet seed hull lodged far up in the upper fornix.

These two cases show how important it is to examine the upper cul-de-sac when suspicion of foreign body exists. A flattened round glass rod lifting the upper border of the everted upper lid under good illumination is the most suitable way of doing this (Fig. 2).

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Aesthesiometer probe tips

A photomicrographic examination

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A corneal aesthesiometer probe made of platinum wire previously described (Larson, 1970) was examined under a microscope after a long period of use to see if any change had taken place in the shape of the tip. Two nylon probes were also examined at the same time.

The photomicrographs (Figure), show two views of the platinum probe made from 0·127 mm. wire (*a*, *b*,), one view of a 0·12 mm. nylon probe (*c*), and two photographs of the same view of a 0·08 mm. nylon probe with normal illumination (*d*) and cross-illumination (*e*).

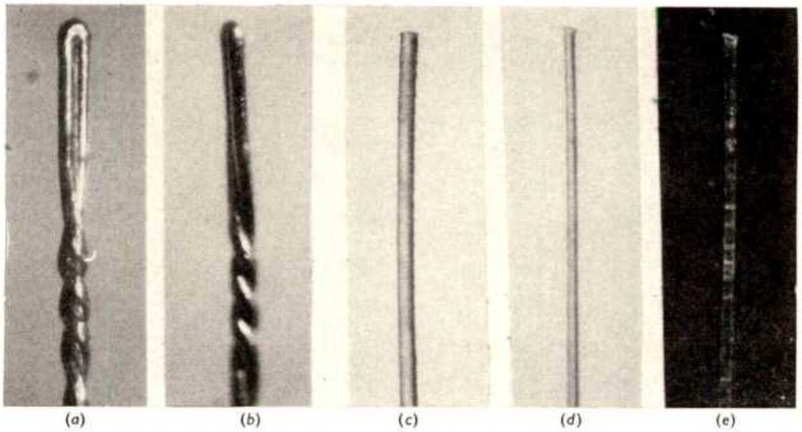

FIGURE *Comparison of platinum and nylon probe tips.* ×32

(*a*) and (*b*) Platinum probe near the tip
(*c*) 0·12 mm. nylon probe
(*d*) and (*e*) 0·08 mm. nylon probe
(*e*) 0·08 mm. probe lighted from the side

The life history of these probes is not fully known. The platinum probe has been in use for 3 years and must have been flame-sterilized several hundred times. The nylon probes are about 4 years old and have been used for research studies.

The pressure distribution in the corneal epithelium caused by the platinum probe can be predicted, because of the uniform, and known, curvature of the tip. Such a prediction is not possible for the nylon tips because the pressure distribution will depend on the angle of incidence of the tip. This is because of the sharp corner where the nylon has been cut. This consideration may be of practical importance and is at present under study.

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The changes in the platinum tip due to flame-sterilization are seen to be insignificant. Barely visible in the photographs is a pattern of shallow pitting on the surface of the metal. No sharp edges have developed and the shape has remained the same.

The condition of the platinum tip, as shown, incidates that the deterioration of the tip shape with repeated sterilization is a very slow process. Until such a time as a reasonable life expectancy for such tips can be established, it is suggested that the tip be examined with a hand-held pocket microscope after every 100 sterilizations.

Experience has shown that this probe does not provoke any corneal injury or irritation and that it can be considered safe for use in corneal aesthesiometers, provided the above examination is regularly performed.

I thank Dr. M. A. Ali of the Département de Biologie, Université de Montréal, for providing partial financial support from his National Research Council of Canada grant.

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Book reviews

The Hereditary Dystrophies of the Posterior Pole of the Eye. By A. F. DEUTMAN. 1971. Pp. 484, 263 photographs, refs. Royal Vangorcum, Assen, Netherlands (Hfl. 146)

Medical authors, writing about pathological entities may often be divided into "lumpers" and "splitters". The former tend to take all conditions which look alike and classify them together, while the "splitters" finely compartmentalize disorders often with the result that similar-looking entities are given multiple names. In no field is there more confusion than that of the disorders affecting the posterior pole of the eye. Deutman, in this beautifully produced and illustrated volume which is apparently an M.D. thesis, has attempted to categorize rationally hereditary disorders of the posterior pole. By virtue of prodigious labour, both by directly observing hundreds of patients and examining the world literature on the subject, he has given us a volume which will be the cornerstone for future endeavour in this field. The author turns out (for the most part) to be a "splitter", and he gives firm evidence for separately classifying sex-linked juvenile retinoschisis, vitelliform dystrophy, and, perhaps, Stargaardt's disease, as well as less common entities such as dominant progressive foveal dystrophy, reticular dystrophy of the retinal pigment epithelium (Sjogren), and butterfly-shaped pigment dystrophy. Less successful, for this reviewer, were the chapters dealing with drusen and fundus flavimaculatus.

All modern modalities of diagnostic testing are utilized in assisting with correct diagnosis. Included for each disorder are the results of electrophysiological testing, psycho-physical testing, spectral retinal photography, and fluorescein angiography. By means of these examinations it has been possible to determine which level of tissue at the posterior pole is involved initially in the pathological process.

One point that is rather disquieting is the author's use of the term "fovea" where most ophthalmologists would use the word "macula". Though there is, in the introductory chapter, the explanation for this usage, it is rather confusing, and anyone not starting from this initial chapter may be extremely puzzled. The numbering of the illustrations is also unfortunate; they are neither sequential nor labelled to show the chapter of origin. Several figures are unlabelled (such as the picture on page 15) or mislabelled (such as figures 1–7 on page 107 and figures 2–4 on page 327).

All in all this volume is highly recommended for anyone interested in macular disorders, and that should, presumably, include all ophthalmologists.

Viruses and Uveitis (Virus et uvéites). By C. MARTENET. 1971. Pp. 136, Figs, Tables, Refs. Doin, Paris. (Frcs 65)

The great majority of patients with uveitis show no evidence of a generalized systemic infection. and uveitis is a rare complication of infectious fevers of viral origin. The suspicion remains, however, that viral infections could be responsible for uveitis in the absence of obvious systemic manifestations. The careful clinical studies described in this monograph, in which the serum and, in many cases, the aqueous were examined for the presence of antibodies to a variety of viruses, lend little support for this suspicion. Out of 170 cases of uveitis, a viral aetiology was considered proved in five cases of herpes simplex, three of herpes zoster, and one of varicella. A rickettsial aetiology was suspected in an Egyptian patient, adenovirus infection in four other cases, infectious mononucleosis in two with papillitis, and influenza in one.

Although the results can only be considered disappointing, this has been a valuable study. The experimental work on herpes infection in the rabbit confirmed that local antibody production can take place in the eye and that infection of one eye can lead to a uveitis in the opposite eye.

The first part of this monograph contains an excellent review of the characteristics of the viruses known or thought to cause ocular disease and the literature concerning the clinical characteristics of viral uveitis, and the work ends with a brief discussion of treatment.

Manual of Tonography. By R. C. DREWS. 1971. Pp. 128, 89 figs, refs. Mosby, St. Louis; Kimpton, London. (£6.20)

The writer of this review holds some beliefs which are opposed to those of the author of this book, who states in his preface "To deny patients tonography is to set glaucoma care back 20 years". It has to be admitted, therefore, that the reviewer could not read the book without challenging the author to convert him from his disbelief, and it is to be hoped that the reviewer has not been unreasonably resistant to conversion.

The book starts off with a brief but interesting history of tonography, and this is followed by a short adequate account of the theory of tonography, including such matters as ocular rigidity. The basic errors of tonography are mentioned, mathematics being kept to a minimum—which is a good idea in a book concerned largely with clinical applications. It is pleasing to find that the routine correction of tonographical results for abnormal ocular rigidity is not recommended, because there is evidence that such corrections are not always valid.

There is a very useful section dealing with the equipment needed for tonography. This includes not only such obvious things as the various electronic tonometers and recorders, which are dealt with in some detail, but also other necessary items, such as something for the patient to lie on and something for the technician to sit on. These less obvious items are worth mentioning, because anyone who wants to do tonography properly will have to acquire everything that is needed, and the initial cost needs to be worked out carefully. Not only the money required has to be considered but also the space, and this point is also made. In fact, the author draws up a table of costs (unfortunately in dollars only) and makes no secret of the fact that a tonography unit is not cheap either to set up or to maintain and operate. His comments regarding the technician who is to use the equipment and do the tests are excellent; you must have somebody who is kind, intelligent and reliable. The section on the practice of tonography is clearly written and full of sound advice and is very useful not only to clinicians but also to the technicians who will do the tests.

In all the above respects this book is to be recommended, but, in the reviewer's opinion, it is disappointing when it somes to the problem of the clinical value of tonography as distinct from its undoubted value in research. As already mentioned, tonography is time-consuming expensive (even this book of 128 pages costs £6.20 in Britain). This would not matter if the procedure gave information of vital importance in the management of glaucoma patients and did not use up money and time which, with a limited budget, could perhaps be used on equipment and personnel for testing the visual fields. The author makes repeated statements about the clinical importance of tonography, but his assertions are not equalled in number by the items of factual evidence that tonography really does improve one's ability to diagnose glaucoma and really does prevent sight being lost in the long-term treatment of this condition. The author says that much evidence exists proving the value of tonography but he gives this evidence in general terms only.

The reviewer considers that the author should have devoted a section of this book to a critical and convincing review of this evidence because this would seem to be the best way of achieving the intention stated in the preface that "The purpose of this book is to help patients get better care".

Biochemistry of the Eye. Edited by C. N. GRAYMORE. 1970. Pp. 783, figs, tables refs. Academic Press, London. (£12)

This large volume consists of eight review articles written by ten authors, all authorities on their subject.

The cornea (D. M. Maurice and M. W. Riley), retina (C. N. Graymore), and lens (J. F. R. Kuck Jr.) are dealt with in a similar manner. The metabolism of the tissue is fully described together with the nature of the component proteins and enzymes, and any other substances which have attracted the attention of biochemists. The articles on the lens and retina also describe in detail the biochemical aspects of functional failure, cataracts, and retinal degeneration (hereditary and chemically-induced) respectively.

The cornea and sclera were the subject of a chapter by Maurice in "The Eye", volume 1, "Vegetative Physiology and Biochemistry", 2nd edition, published in 1969, also by the Academic Press. In this publication, Maurice fully reviewed the structure and function of the cornea, and Maurice and Riley have therefore concentrated chiefly on the biochemistry of the tissue.

Metabolism of the retina was also the subject of an article, also by Graymore, in "The Eye", vol. 1, there is considerable overlap between the two chapters, although the "Biochemistry of the Eye" contains a longer and more detailed account.

The lens was dealt with by two different authors in "The Eye", vol. 1. Kuck, whose contribution is divided into three chapters "Chemical constituents of the lens", "Metabolism of the lens", and "Cataract formation", is less informative about recent work on lens proteins, and gives more space to other chemical constituents, such as nucleotides and lipids.

The ciliary body and aqueous humour (D. F. Cole) and the vitreous body (E. R. Berman and M. Voaden) both have their counterparts by different authors in "The Eye", vol. 1. Dr. Coles' contribution is an interesting review of the composition of the aqueous humour and the processes by which it is formed and leaves the eye. Surprisingly little research has been done on the ciliary body itself, probably because it is difficult to isolate and to dissect with pigmented and non-pigmented layers. This important tissue deserves more attention from the biochemist. The chapter in the vitreous body is a full account of the structural aspects of and the movement of fluids and solutes through the structure.

Biochemistry of vision (C. D. B. Bridges) is a detalied review of present knowledge of all aspects of the visual pigments, in solution and in the eye, their nature, distribution, photo products, and changes associated with bleaching.

Unlike the others, the last two chapters are not concerned with one part of the eye, but with the effect upon the whole organ of inborn errors of metabolism in man (C. N. Graymore and D. Y. Y. Hsia) and of malnutrition, chiefly vitamin deficiency, in man and animals (D. S. McClaren). Neither chapter has much to say about the biochemistry of the eye, but this is not a criticism; very little is known about this aspect of the subject. Inborn errors are a fashionable topic and research on the subject is abundant. Nutritional research is not so fashionable, being frequently tedious and difficult. It may be in this field that the most important advances, in terms of benefit to mankind, are to be made; this chapter serves to emphasize how sketchy is our knowledge of the subject at the present time.

This book, which reaches a consistently high standard, will be valuable to research workers with an interest in any part of the eye, and essential for newcomers to the field. Apart from the important matter of expense to libraries or individuals, such comprehensive articles are time-consuming to write, and Academic Press are to be criticized for commissioning two similar volumes at almost the same time.

As the Editor points out, this is the third book to be entitled "Biochemistry of the Eye". The first (264 pages) was written by one author in the thirties, the second (323 pages) by two authors in the fifties, and this one (783 pages in 1970 is by ten authors. It will surely be the last attempt to cover the whole subject in one volume.

Strabismus, Heterophoria, Ocular Motor Paralysis (Clinical Ocular Muscle Imbalance) (Strabismes, hétérophories, paralysies oculo-motrices (Les déséquilibres oculo-moteurs en clinical)). By R. Hugonnier and S. Hugonnier. 3rd ed., 1970. Pp. 866, 270 figs. Masson, Paris. (Frs 130)

France has a reputation for producing men who have made valuable contributions to our knowledge of strabismus and its treatment, among whom in the past have been Javal Remy, Onfray, and Cantonnet and Filoziat. It is therefore most appropriate that another Frenchman has continued this tradition by writing a good textbook on the subject of strabsimus. He is assisted in this work by his wife, who is a distinguished orthoptist.

That a third edition of this book has been necessary so soon (the second edition was published in 1965) speaks for itself. There is no doubt that in the majority of European countries it is the most popular book on the subject.

The text has the great merit of being comprehensive. It covers a brief history of the subject and a short discourse on terminology before the main text begins, which is tidily divided into six parts.

The first part consists of a clear and well-illustrated exposition on relevant anatomy and physiology.

The second part deals with generalities about concomitant squint and heterophoria including the mechanism of abnormal retinal correspondence and amblyopia.

In the third part oculomotor paralysis is studied in depth, including the acquired as well as the congenital forms of this anomaly. Retraction syndromes and pseudostrabismus are also dealt with.

The fourth part is devoted to methods of examination and is extremely well written.

The fifth part is devoted to treatment and deals with general medical treatment, optical treatment including the use of prisms, the treatment of amblyopia, and orthoptic treatment.

The sixth part deals with surgical treatment and is well illustrated by drawings which in the majority of cases are so much easier for the student to understand than photographs. There is much useful information on the indications for operation in the various forms of strabismus including the indications for surgical treatment in cases of nystagmus associated with a compensatory head posture.

An unusual feature of the book is the appearance of the list and details of the contents at the end instead of at the beginning, which would be more usual and perhaps preferable. However, this arrangement means that the first thing to catch the eye of the reader on opening the book is a delightful article entitled "some aphorisms" which comprises many well-known statements and others less well-known but none the less true, such as that of Chavasse, who said "An orthoptic department must be diagnostic before it can pretend to be therapeutic".

There is no list of references, but in many ways this is a good idea since the book is based on broad general principles and any list of references mught tend to be incomplete or else so long that it would take up too much room.

The authors are to be warmly congratulated on the third edition of their book and we look forward to its English edition shortly.

Measurement of Ocular Muscle Imbalance (Mesure des déséquilibres oculo-moteurs par la méthode des formes à choix). By J. B. WEISS. 1971. Pp. 92, figs, bibl. Doin, Paris.

The author has devised a test of muscle balance very similar to the Hess test. He has added a pattern of dots visible to each eye despite the red and green goggles, so that some stimulus to fusion exists. The test can be used without the dots (*forme libre*) or with the dots (*forme à choix multiple*) and the result is plotted on a chart similar to that used for the Hess test. The results of the two tests in phorias, tropias, nystagmus, refractive errors, and a few miscellaneous conditions are presented. In some cases the results are similar, in others dissimilar. The authors explain the disparity by the intervention of fusion or accommodative mechanisms. The significance of this is not explained and the advantages of this new technique are not made apparent.

Practical Atlas of the Surgery of Strabismus. Operative Indications, Surgical Technique (Atlas pratique de la chirurgie du strabisme. Indications opératoires. Technique chirugicale). By F. HERVOUËT with the collaboration of A. MEGROZ. 1970. Pp. 418, figs, bibl. Masson, Paris. (Frs 200)

This is a beautifully illustrated book showing typical clinical examples of the various types of strabismus and oculomotor anomaly, outlining the clinical facts, the treatment carried out, the progress of each patient, the final result, and comments on management.

In this book the reader will find examples of every common condition of strabismus that he is likely to meet.

The chapter dealing with surgical technique is particularly well illustrated with large clear photographs which are truly unique in their excellence.

It is nice to see a chapter devoted to the complications and the sometimes "disappointing" results of surgery in cases of strabismus, and it is also refreshing to find a chapter dealing with the relationship of the ophthalmologist with the parents of a child suffering from squint, with the patient himself, with the orthoptist, and with his medical colleagues. This chapter also includes information on the postoperative care of the patient.

The author rightly pays a warm tribute to the work of Hugonnier, whose photograph adorns the last page.

Notes

IV International Ergophthalmological Symposium

Budapest, April 16, 1972

The IV International Ergophthalmological Symposium will be held in Budapest in association with the IVth Congress of the European Society of Ophthalmology, on April 16, 1972, at 9.30 a.m. The main subjects will be:

(1) The requirements of visual efficiency of workers with and without protective goggles.

(2) Illumination for work.

(3) Rehabilitation of the visually handicapped.

Those wishing to participate should apply as soon as possible to the general secretary:

Prof. Dr. Enrique López Quinones, Leibnitz 47–403 Mexico 5 D.F., Mexico

or to the European secretary:

Dr. L. Toppel, Augenklinik rechts der Isar, Technischen Universität Munchen, 8000 *Munchen* 80, Ismaninger Strasse 22, Germany.

II International Medical Congress on Ultrasonics

Rotterdam, June 4 *to* 8, 1973

The Second World Congress on Ultrasonics in Medicine will be held from June 4 to 8, 1973 in 'de Doelen' Congress Centre in Rotterdam, under the Chairmanship of the Dutch neurologist, Dr. M. de Vlieger, and under the auspices of the Medical Faculty at Rotterdam and the World Federation for Ultrasound in Medicine and Biology.

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For further information please write to the secretariat of the 2nd World Congress on Ultrasonics in Medicine, Holland Organizing Centre, 16 Lange Voorhout, The Hague, Netherlands.

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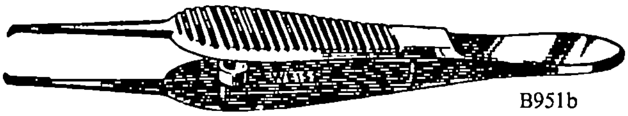

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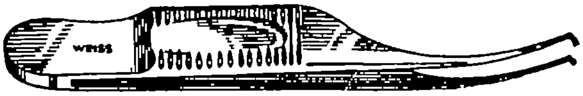

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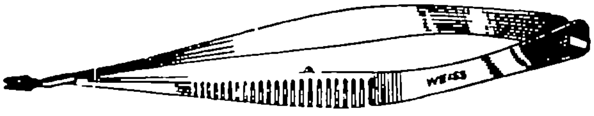

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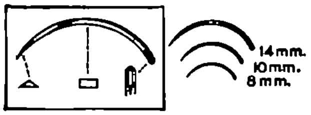
B874. **Forceps,** corneal, Barraquer's *do.*
B1053. **Scissors,** miniature, for removal of corneal sutures, etc.



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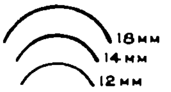

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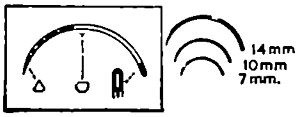

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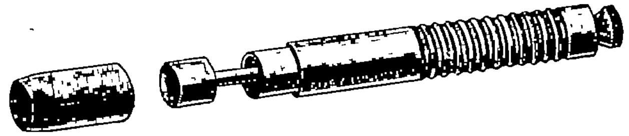

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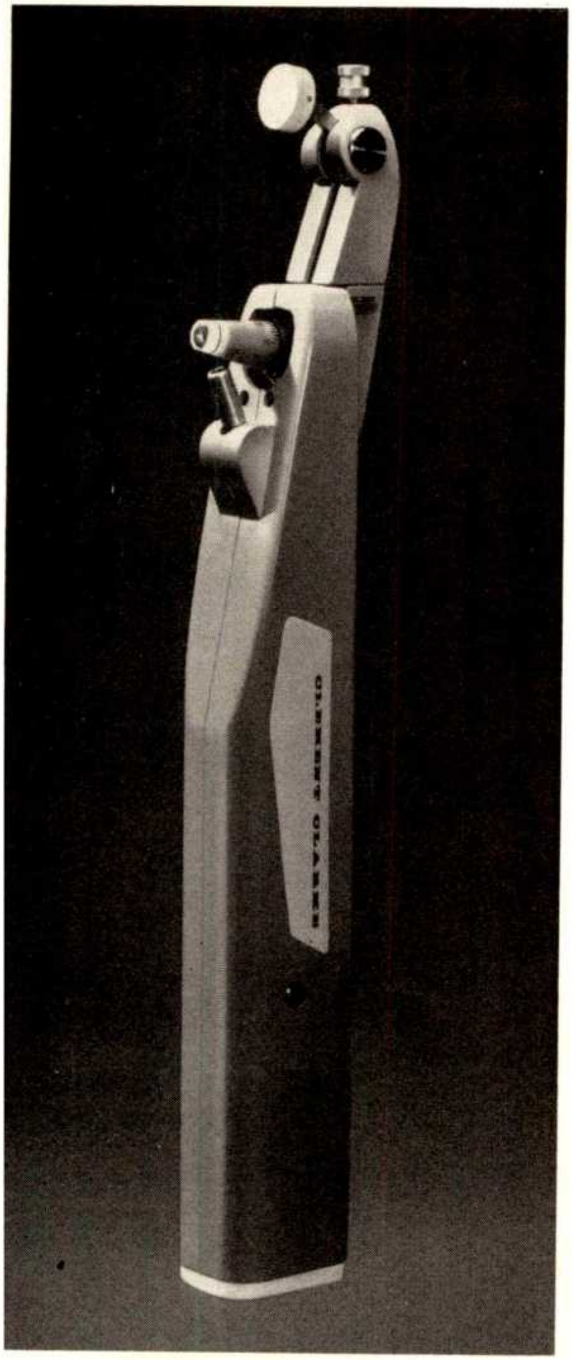

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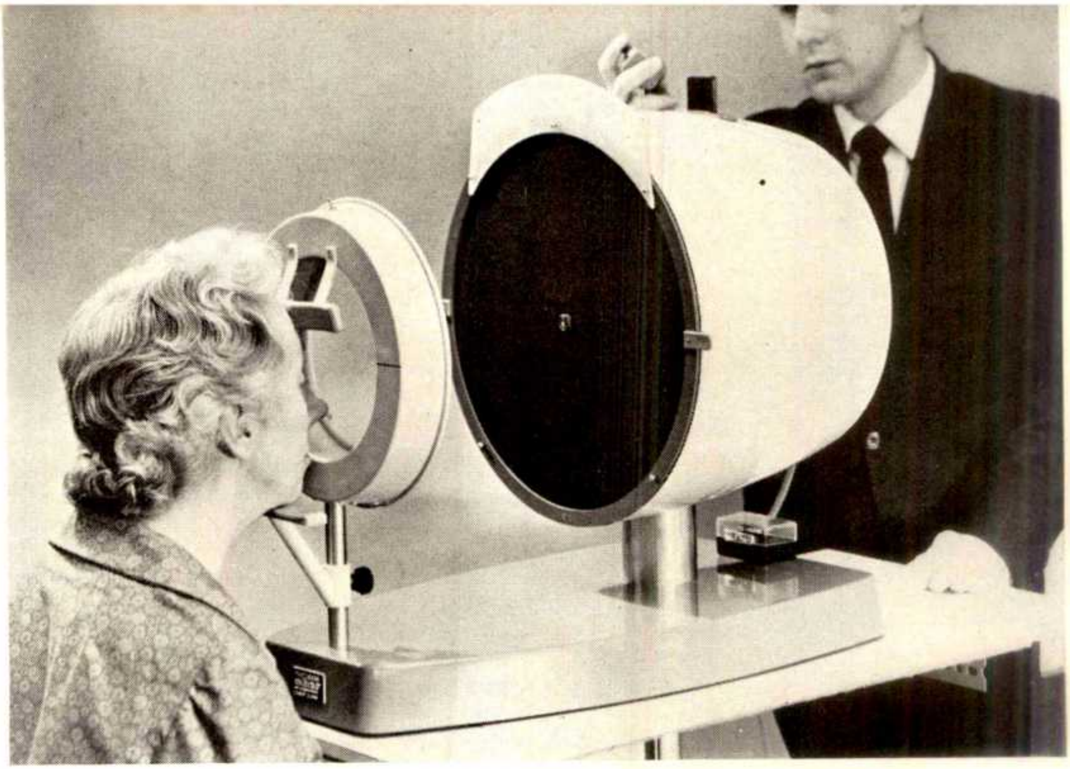

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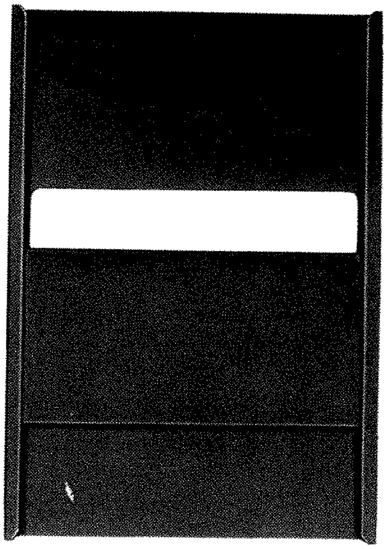

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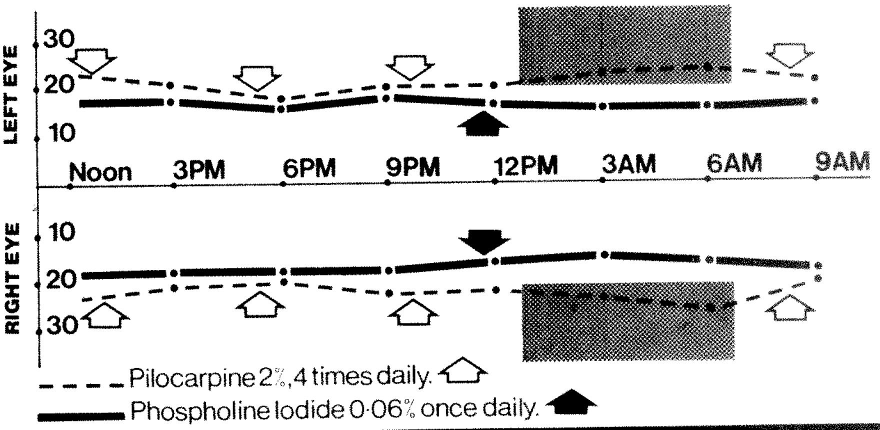

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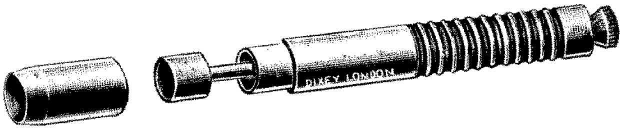

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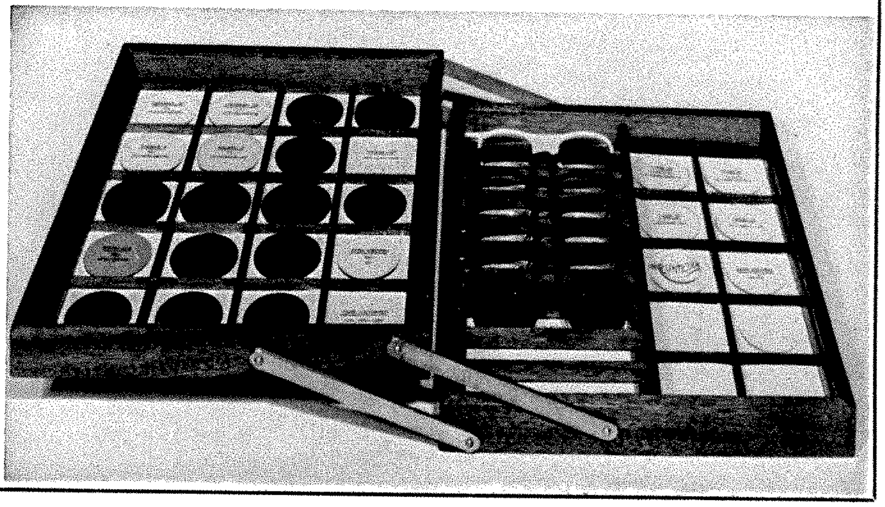

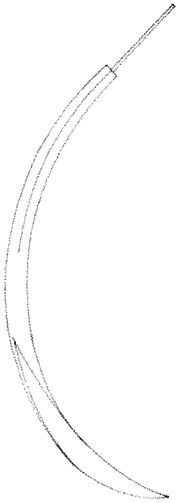

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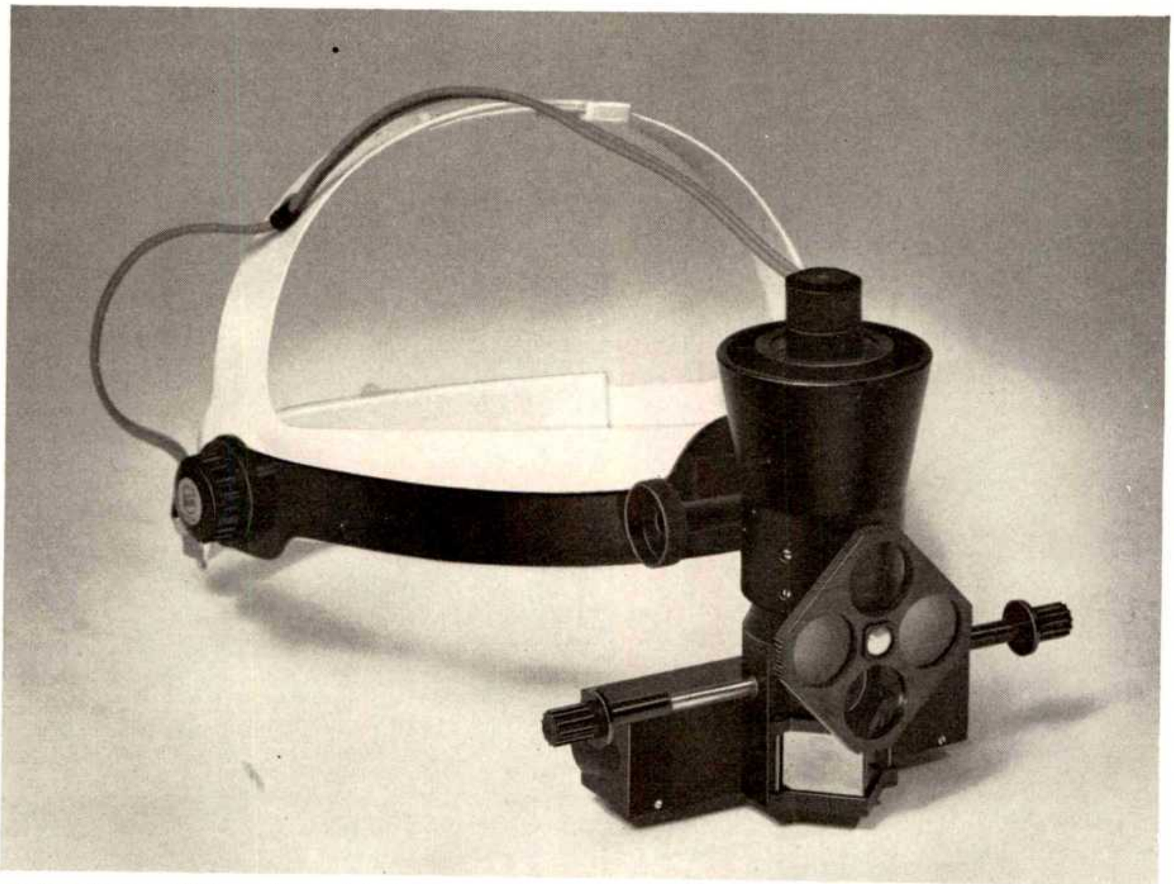

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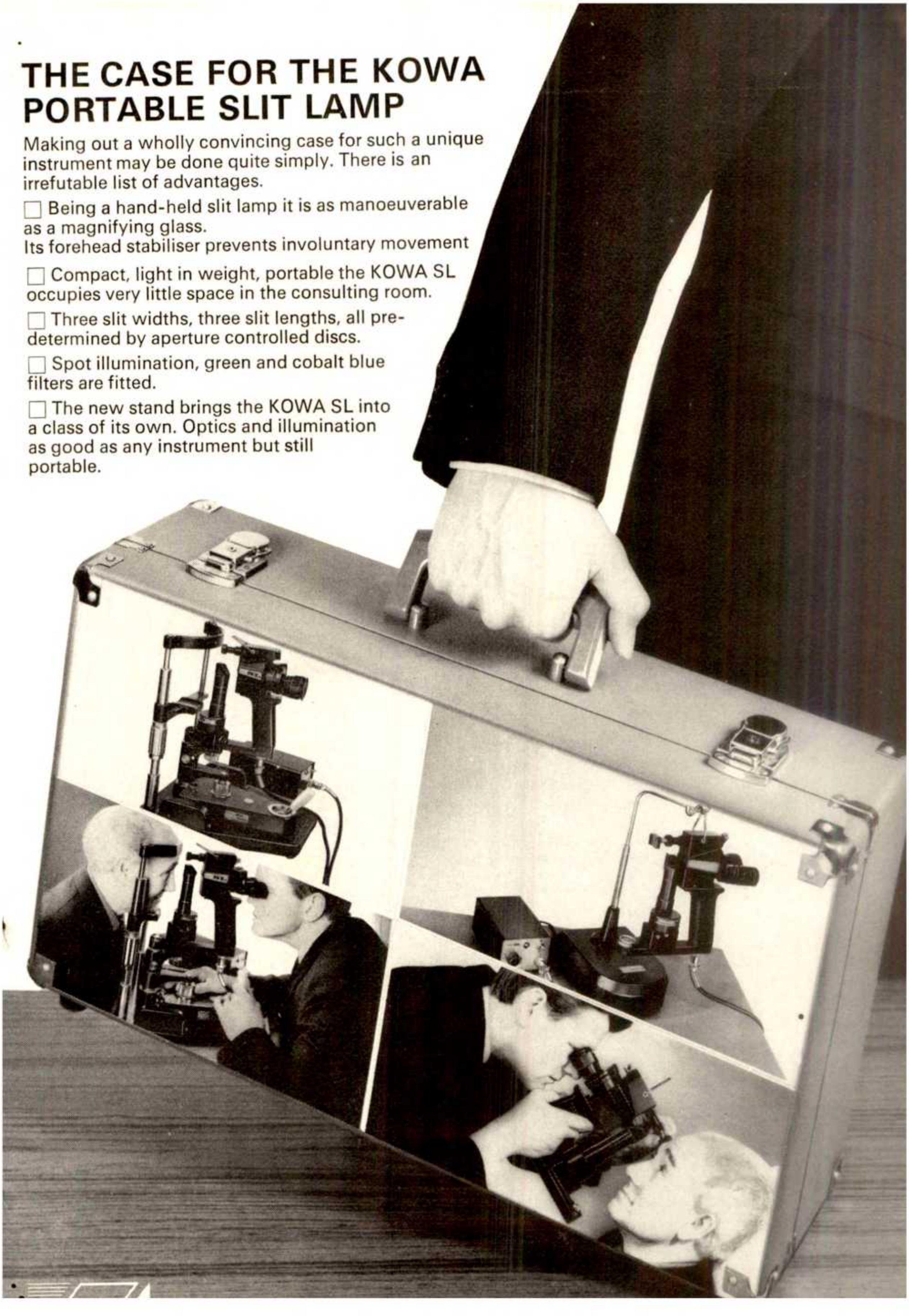

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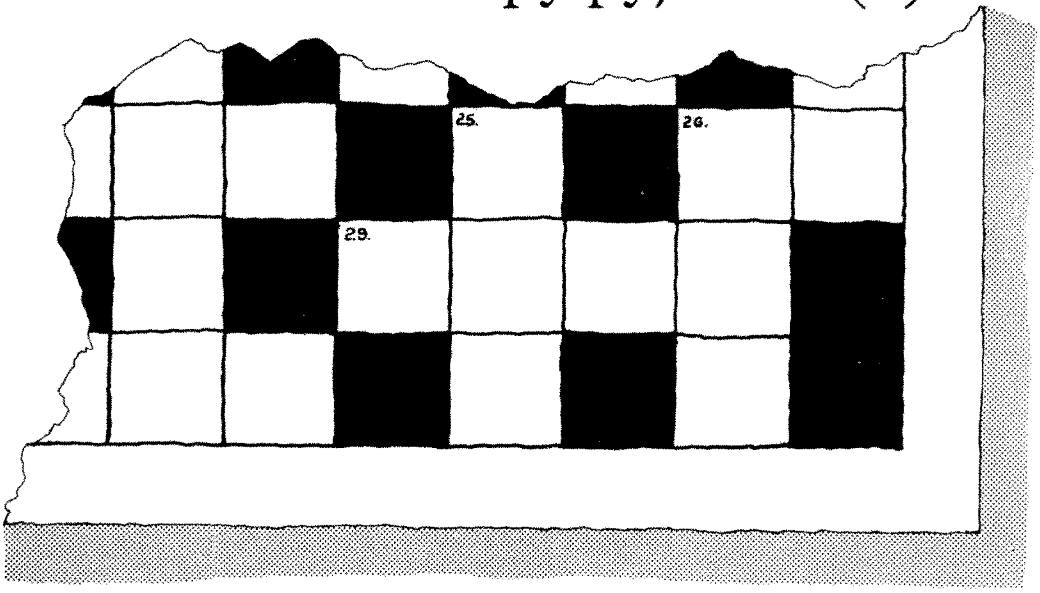

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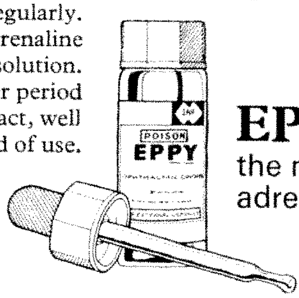

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Communications

Autoimmune reactions in uveal melanoma

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Choroidal melanomas may remain localized for more than 30 years (Newton, 1965); malignant melanomas of the iris may not metastasize at all (Ashton, 1964), and some of these intraocular neoplasms may undergo spontaneous regression (Fuchs, 1910). From time to time several hypotheses have been advanced in an attempt to explain these puzzling features of the behaviour of uveal melanomas. Furth (1953) first proposed that melanomas are tumours conditioned by changes in host environment. Dunphy (1957) then elaborated the theory of "defensive substances" present in the body which prevented a uveal melanoma from disseminating into the general circulation. Anderson and O'Neill (1957) referred to these substances as "biochemical barriers". This concept was supported by Reese (1963), who stated that certain "unknown factors", probably immunological in nature, kept the tumour dormant for a long time or inhibited their growth completely, metastases developing only when there was a breakdown in the immunity of the host. Jensen (1963), in his thesis on uveal melanomas, upheld the views of earlier workers and argued that variations in metastases, such as their frequency, temporal relationship, latency, and in certain cases spontaneous necrosis, suggested the existence of such factors as immunization and resistance. Duke-Elder and Perkins (1966) appeared to favour this hypothesis, thus explaining infrequent and delayed metastases in spite of the early dissemination of tumour cells in the blood stream. Such a latency is not peculiar to ocular melanomas and in fact several instances of dormant cancers of the breast, kidney, etc., are on record (Gordon-Taylor, 1959). To explain dormancy and spontaneous regression, Burnet (1964, 1967) suggested that the homograft rejection phenomenon was essentially a homeostatic mechanism to eliminate cells of any clone undergoing malignancy, and since a neoplastic cell carried a new surface antigen it might be destroyed by a similar mechanism to graft rejection. It is now believed that cancers probably develop and proliferate as a result of a failure in the equilibrium between the spontaneous proliferation of neoplastic cells and the ability of the body's immune mechanism to control this process (Turk, 1969). The role of immunological processes in the control and development of malignant neoplasms has been appreciated only in the last few years, although it has been suspected since the work of Simon and Thomas (1908). Foley (1953) is considered to be the first to have demonstrated specific antigenicity of chemically induced tumours. This was most closely anticipated by the work of Gross (1943) who demonstrated active immunization in C3H mice to transplants of early methyl-cholanthrene-induced tumours. Reports of tumour immunity before this time could not be accepted, as these earlier experiments had been conducted either in animals of unproven homogeneity or with tumours that had been transplanted for

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long periods (Hauschka, 1952). Malignant cells do not appear to be recognized as self, either because of loss of normal tissue-specific antigens, as seen in thyroid carcinomas, or because of the acquisition of new (tumour-specific) antigens as found in nearly all experimental tumours (Alexander and Hall, 1970). The new antigen in chemically induced tumours is so individually specific that it will not cross-react with tumour antigens from other animals, in which the neoplasm was induced by the same chemical (Prehn and Main, 1957; Old, Boyse, Clarke, and Carswell, 1962). Thus, there is no correlation between the antigenic nature of the tumour and the chemical which induces the neoplasm, even in two tumours induced by the same agent in the same animal. On the contrary, tumours induced by viruses (*i.e.* RNA viruses—Rous Sarcoma virus; oncogenic DNA viruses—polyoma viruses, SV40 virus, and adenoviruses—type 3, 7, 12, 18, 31) in a wide selection of animals (chicken, mice, monkeys, hamsters) possess specific antigens for the causative virus, irrespective of the species or strain of animal used (Defendi, 1963; Trentin and Bryan, 1964; Huebner, Rowe, Turner, and Lane, 1963). The only exception to the rule are hybrids formed by adenotype 7 with SV40 (Rowe and Baum, 1964). This general pattern is so constant as to suggest that certain human tumours, like Burkitt's lymphoma and leukaemia, may have a viral origin, and in fact EB virus has been demonstrated in the former (Epstein, 1970). Tumour antigens appear very early in the process of carcinogenesis and may occur even in the precancerous stage (Turk, 1969), as evidenced by suppressed cellular immunity in leukoplakia (Lehner, 1970). How these antigens appear is a matter of conjecture. Either there occurs a spontaneous mutation or, in the wake of neoplastic differentiation, there is apparently a sudden expression of certain suppressed antigens present in all normal cells. The findings that tumour-specific antigens cross-react with antigens present in embryonic tissue, but normally absent in the fully mature animal, is consistent with the latter view that these antigens appear by a process of de-differentiation rather than by mutation (Gold and Freedman, 1965). If the tumour contains antigens which are not recognized by a central immune mechanism as being part of self, the body will react against them, either by elaborating antibodies which neutralize or destroy, with or without complement, the antigens circulating free or fixed to cell membranes; or by a cell-mediated immune response, in which case sensitized lymphocytes, developed in thymus-dependent areas of lymph node and spleen, invade the tumour to produce an inflammatory response similar to that seen in failed corneal graft or any other allogeneic tissue rejection. Gorer (1961) has divided the effector mechanism of immunological reactions against tumour tissue into three categories:

(1) The humoral antibody which, together with complement, can destroy tumour cells;

(2) The macrophages which are sometimes capable of destroying tumour cells (ascitic tumours) with the help of opsonizing antibodies;

(3) The cytotoxic lymphoid cells acting in the same way as in the rejection of homografts.

It is possible that *in vivo* all these factors work in combination, the first two predominating in lymphomas, leukaemia, ascitic tumours, and haematogenous spread of solid tumours, and the third predominating in the rejection of solid tumours. Concrete evidence that immunology plays an important role in the control of tumours, including uveal melanomas, can be found in the study of experimental tumours and also in their human counterparts.

The evidence of tumour immunity in animals may be summarized as follows:

(1) Mice immunized against chemically induced tumours from another syngeneic mouse by repeated injections of irradiated, but otherwise viable, tumour cells, resist transplantation of the same tumour at a later date (Revesz, 1960; Old and others, 1962).

(2) In the case of virus-induced tumours, animals actively immunized with the virus become resistant to subsequent challenge with tumours induced by the same virus (Sjögren, Hellström, and Klein, 1961; Sachs, 1962).

(3) Animals showing spontaneous regression of tumours become resistant to further transplants of the same tumour.

(4) Actively immunized animals contain antibodies in their serum which are cytotoxic to tumour cells *in vitro*. Intravenous injection of lymphocytes from the thoracic duct of rats, specifically immunized against a tumour, can protect other rats from the growth of that tumour transplanted into them (Delorme and Alexander, 1964). Similarly, when tumour cells mixed with immune cells in a 1 : 1 ratio are injected subcutaneously in a histocompatible normal recipient, there is complete suppression of the grafted tumour (Klein and Sjögren, 1960; Old and others, 1962).

(5) Mice with a depressed immune response or a poor immune surveillance mechanism, *i.e.* those subjected to antilymphocytic serum or neonatal thymectomy, show a significant increase in neoplastic lesions (Law, 1965). Similarly, mice suffering from "graft versus host" disease invariably develop lymphoid tissue tumours resembling Hodgkin's disease.

(6) Polycyclic hydrocarbons (3-methylcholanthrene; 1, 2–5, 6-benzanthracene) are potent carcinogens as well as immunosuppressive agents. These compounds produce leukaemia only in those strains of mice in which they can induce immunosuppression.

(7) Rats with chemically induced fibrosarcoma do not show blood-borne metastasis until antibody has been removed from the circulation (Alexander and Hall, 1970).

There is varied and abundant evidence of similar immunological control in man and the vast literature on the subject may be summarized as follows:

(1) The incidence of neoplasms increases with age, whereas ability to produce cell-mediated immune responses (delayed hypersensitivity) to antigens like tuberculin decreases with age. This diminished activity has been well documented in a recent survey on skin test reactivity of patients with uveitis (Weber and Schlaegel, 1969).

(2) There is an impaired capacity of cancer patients with advanced disease to reject homografts and to develop skin reactions of the delayed type (Southam, 1967). Anergy in Hodgkins disease and diminished humoral antibody response in lymphomas is well documented (Miller, 1965).

(3) Immunization of tumour patients with their own tumour tissue, with or without systemic adjuvant, has been found to increase specific antibody response and their survival rate (Mathé, 1969).

(4) Convalescent sera from cases of Burkitt's tumour, when transfused into other patients, induce tumour regression lasting for several weeks. Similarly, sera from patients showing spontaneous regression of malignant melanoma can induce regression in other melanoma patients (Sumner and Foraker, 1960; Teimourian and McCune, 1963; Nathanson, Hall, and Farber, 1967).

(5) Patients with hypogammoglobulinaemia often develop lymphoreticular malignancy (Seligmann, Fudenberg, and Good, 1968).

(6) Immune suppression with antilymphocytic serum increases the incidence of lymphoma (Sell, 1969).

(7) Recently, a case has been reported in which a reticulum cell sarcoma developed at the site of injection of antilymphocytic serum (Deodhar, Zuklinca, Vidt, Robertson, and Hazard, 1969).

(8) Antibodies to skin melanomas (Lewis, Ikonopisov, Nairn, Phillips, Fairley, Bodenham, and Alexander, 1969), gynaecological tumours (Graham and Graham, 1955), and breast cancers (Taylor and Odili, 1970), have been successfully demonstrated in several cases.

(9) Spontaneous regression of some human tumours like melanomas, hypernephromas, neuroblastomas, choriocarcinomas, and Burkitt's tumours, are on record (Brunschwig, 1963; Everson, 1964; Everson and Cole, 1966; Boyd, 1966).

(10) Lymphocytic infiltration of tumours is a good prognostic sign and correlates well with survival data available for breast cancer (Black, 1965; Hamlin, 1968; Bell, Friedell, and Goldenberg, 1969), gynaecological tumours (Graham, 1957), and neuroblastomas (Martin and Beckwith, 1968) and neoplasms of the digestive tract (Black and Speer, 1958).

(11) Very late recurrence in the case of some tumours (uveal melanomas) and the so-called dormant cancers (Hadfield, 1954) are well-recognized phenomena.

(12) Patients with cancer show a slight increase in the incidence of a second cancer as compared to the normal population. People suffering from leukaemia, for instance, often develop malignancy of other organs.

(13) Removal of a primary tumour sometimes helps in the regression of secondaries (Walter and Israel, 1970), perhaps because of the release of immunoblasts which were in an immobilized state in the presence of the primary tumour (Alexander and Hall, 1970).

(14) Leucocytes from a patient immunized against a tumour (*i.e.* melanoma) help remission when injected into the donor against whose tumour the sensitized leucocytes were produced (Nadler and Moore, 1966).

(15) Large numbers of tumour cells may be found in the peripheral circulation without the development of metastases (Moore, Sandberg, and Schubarg, 1957).

(16) Cellular immunity against tumours of urinary bladder, nasopharynx and other organs has been demonstrated by several independent workers (Hellström and Hellström, 1967; Bubeník, Perlmann, Helmstein, and Moberger, 1970; Chu, Stjernswärd, Clifford, and Klein, 1967).

The above experimental and clinical studies, therefore, suggest that the association between the tumour growth and the immune response of the host is more than casual. Although several suggestions have been made in the past to explain delayed metastases, spontaneous necrosis, and regression in the case of uveal melanomas, no specific immunological reactions have so far been demonstrated in such patients. The present study was, therefore, undertaken to determine whether specific humoral immune responses are involved in such patients. The effect of patients' own sera on the growth and metabolism of their tumour cells was studied *in vitro* and the site of immune reaction was localized by immunofluorescence.

Experimental methods

Immediately after enucleation the eyes were placed in sterile culture medium 199 containing penicillin (200 units/ml.) and streptomycin (100 μg./ml.) as preservative. 20 ml. blood were also collected at the time of operation. The specimens were then transported at ambient temperatures to the laboratory on the same day and in most cases within 2 hours. Sera so obtained were inactivated at 56°C. for 30 minutes and stored at −30°C. As source of complement, serum from a donor with AB group was obtained and similarly stored in 2-ml. aliquots at −30°C. Eyes were orientated and opened by either vertical or horizontal section in the manner described by Ashton (1967). One half of the globe was processed for routine paraffin and celloidin sections and the other half was used for preparing cell suspensions. The tumour tissue was dispersed in T.C. 199 mechanically by scissors and scalpel. Trypsin was not used as its effect on surface antigen is not known, and, moreover, it has been found to expose otherwise hidden antigenic sites (Irvine, 1962) perhaps by digesting away some of the surface glycoproteins (Burger and Noonan, 1970). The viability of tumour cells was analysed by dye-exclusion tests, using 0·2 per cent. aqueous trypan blue. The cell count was finally adjusted to 1 million cells per ml. in T.C. 199 with 20 per cent. inactivated foetal bovine serum. Blood samples from 21 cases of uveal melanoma were tested for antibodies against their own tumours by a culture technique and, where possible, by immunofluorescence and RNA synthesis inhibition tests.

(A) COMPLEMENT-DEPENDENT CYTOXICITY TEST

The method adopted was essentially that of Pulvertaft, Doniach, Roitt, and Hudson (1959) for demonstrating the autoaggressive nature of thyroid autoantibodies in Hashimoto's disease. Cells dispersed in nutrient medium containing normal human serum rapidly become attached to the glass wall of the culture chamber. In the presence of specific antibodies and complement, a cytotoxic effect is obtained and the cells fail to attach to the glass surface. Essentially, cytotoxicity is recognized by failure of tumour cells to continue to adhere and grow on the cover glass, which seals the top of a special culture chamber made of a Teflon ring stuck to a microscope slide by silicone grease. With each tumour three tests were set up. To each chamber 1 ml. cell suspension was added and then topped up with:

(*i*) 1 ml. normal serum containing complement;
(*ii*) 1 ml. inactivated patient's serum;
(*iii*) 0·5 ml. patient's serum + 0·5 ml. complement.

The chambers were then sealed by coverslips, avoiding any air bubbles, and were incubated at 37°C., inverted (*i.e.* coverslip down) for the first 48 hours and then right side up for the next 2 to 5 days. The chambers were examined under contrast phase microscopy, and a serum was recorded as being cytotoxic when chamber (*iii*) showed very little or no growth as compared to chambers (*i*) and (*ii*). In the absence of growth an estimate was made of the relative number of cells adhering to the cover glass in all the three chambers, and this was later verified after fixation in alcohol-ether mixture and staining with haematoxylin and eosin. Degrees of cytotoxicity were then assessed in terms of the cytological changes in fixed cells.

(B) COMPLEMENT-DEPENDENT INHIBITION OF RNA

The effect of patients' serum (in the presence of complement) on ribonucleic acid (RNA) synthesis was assessed by the capacity of tumour cells to incorporate radioactive uridine (Lewis and others, 1969). RNA synthesis is greatly reduced when the cell is damaged by cytoxic antibodies in the presence of complement. 1 ml. cell suspension containing 5 million cells in T.C. 199 was put into each of the three tubes and the following were then added:

Tube 1—1 ml. normal serum with complement;
Tube 2—1 ml. patient's inactivated serum;
Tube 3—0·5 ml. patient's serum + 0·5 ml. complement.

The mixture was incubated at 37°C. in a water bath for 1 hour and then 2 μCi (3 Ci/mM) tritiated uridine was added to each tube and incubated for a further period of 1 hour. At the end of incubation the tubes were chilled and then centrifuged. To the deposit 5 per cent. trichloracetic acid was added to precipitate proteins. After extraction with absolute alcohol, the proteins were digested in normal potassium hydroxide and then mixed in a scintillator NE 233 with solubilizer NE 520, according to the direction of the manufacturers (Nuclear Enterprises, Edinburgh). The radioactivity was then assayed in a Packard tricarb liquid scintillation counter. The count was expressed in terms of net^{3}H uridine uptake in counts per 5 minutes.

The test was regarded as positive if the uptake in Tube 3 was at least 20 per cent. smaller than that in Tubes 1 and 2. A difference of ± 10 per cent. in Tubes 1 and 2 was ignored when interpreting the result.

(C) IMMUNOFLUORESCENCE STUDIES

Immunofluorescent staining of tumour cells was carried out by the sandwich technique (Nairn, 1969). For membrane fluorescence 1 ml. of original cell suspension in T.C. 199 was centrifuged and washed with phosphate buffered saline. The patient's own serum was then added and after incubation at 37°C. for 30 minutes the cells were again centrifuged and washed and fluorescent anti-human immunoglobulin (IgG/IgM) serum was then added. After further incubation for 30 minutes the cells were centrifuged and washed twice in buffered saline. A drop of cell suspension was placed on a clean microscope slide and mounted in buffered glycerol saline. A Vickers fluorescent unit was used for the present study which has an HBO 200 mercury vapour lamp as a light source. UG 2 excitor filter was used with bright field condenser and GG 4 + Wratten E as barrier filter.

For cytoplasmic fluorescence, tumour tissues processes at 4°C. were blocked (in paraffin), sectioned, and stained according to the technique of Sainte-Marie (1962).

In both membrane and cytoplasmic fluorescence, normal sera were used as control; sera from uveal melanoma patients were also tested for cross-reacting antibodies.

Results

(a) Cytotoxicity tests

Of the 21 tumours examined, seven showed the presence of cytotoxic autoantibodies which were active only in the presence of complement (Figs 1, 2, 3, and 4, opposite and overleaf). Three cases reported here as negative showed poor growth in all the chambers.

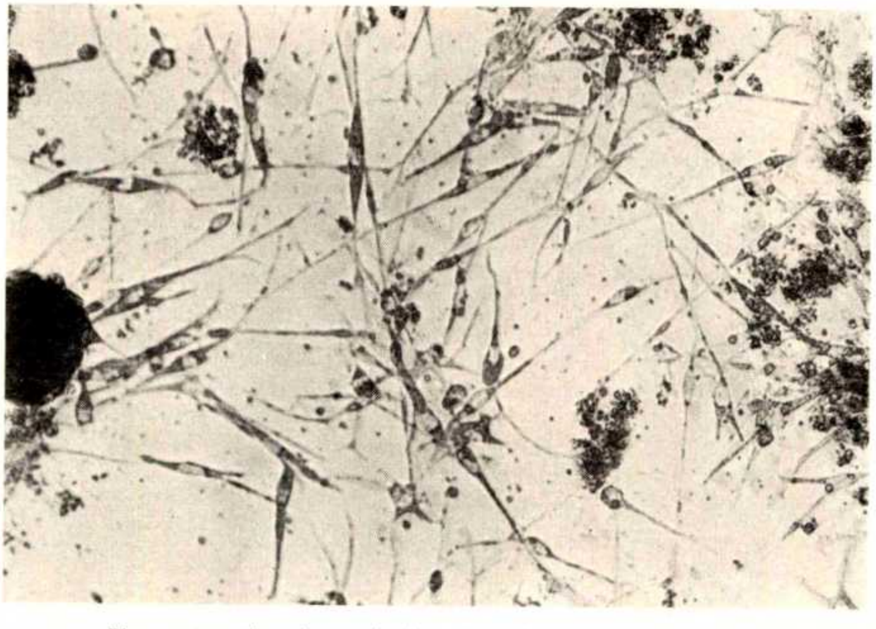

FIG. 1 *a* *Phase-contrast photomicrograph of growing melanoma cells in normal serum.* × 132

(b) RNA synthesis inhibition tests

These were performed in four cases. Positive results were obtained in two cases which had also shown the presence of cytotoxic antibodies by culture technique. In one case positive by the culture technique, the result was inconclusive. One case was negative.

(c) Immunofluorescence tests

Three cytotoxic sera tested for membrane fluorescence against their respective tumours gave positive results; some of the cells, however, in the same preparation also showed

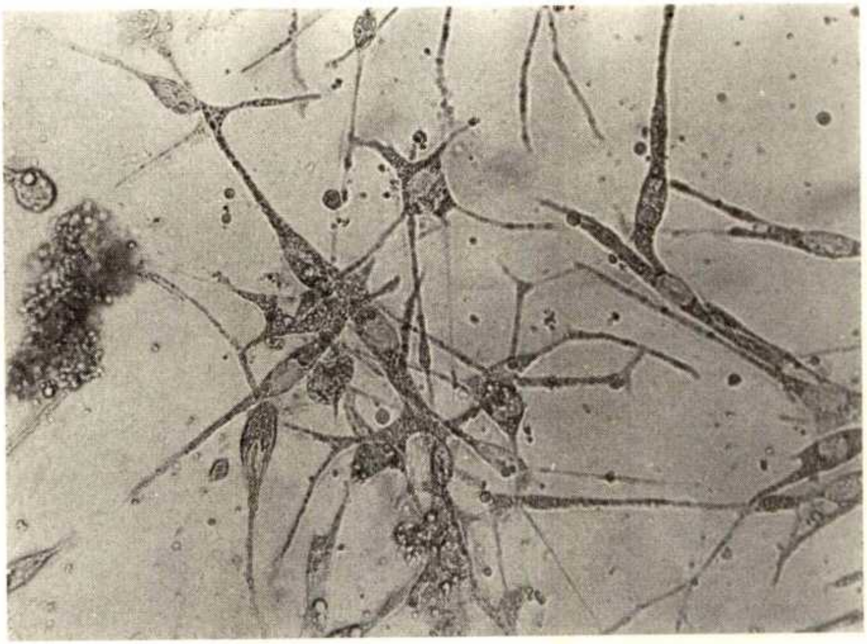

FIG. 1 *b* *Phase-contrast photomicrograph of growing melanoma cells in patient's own decomplemented serum.* ×285

cytoplasmic fluorescence (Fig. 5, overleaf). This was perhaps due to the fact that the cell suspension used in the present test was obtained by mechanical means and, therefore, was a mixture of dead, damaged, and viable cells. During the test a curious phenomenon was noted. Some of the control slides treated with normal serum at times showed fluorescence of a few of the cells. This was attributed either to cross-reacting antibodies in normal serum, or to *in vivo* fixation of autoantibodies on to the tumour cells. Cytoplasmic fluorescence was not observed in histological preparations tested for cross-reacting antibodies, which are believed to be present in skin melanomas (Lewis and others, 1969). The clinical, pathological, and serological data are summarized in the Table (overleaf).

Discussion

It seems certain that at least some human neoplasms possess antigens which are not present in other tissues of the individual bearing the tumour (Taylor and Odili, 1970). These neoantigens are called tumour-specific transplantation antigens (TSTA). It may be recalled that the human body reacts to antigenic stimuli by elaborating specific antibodies where antigen is available in soluble or macromolecular form in the circulation, and by producing aggressive sensitized lymphocytes where the antigen is fixed at a distant site. It is, therefore, natural to find both humoral and cellular responses in human cancers (Klein and Oettgen, 1969), the first produced against circulating tumour components and the second against the fixed tumour antigens, as in the case of solid tumours. Both these effector mechanisms are important for the control of tumour growth. A solid tumour may be infiltrated by lymphocytes, which limit its growth by reacting directly with tumour-specific antigens or perhaps by the local secretion of certain toxic substances which are collectively called lymphokines (Dumonde, 1970). The circulating tumour cells, on the

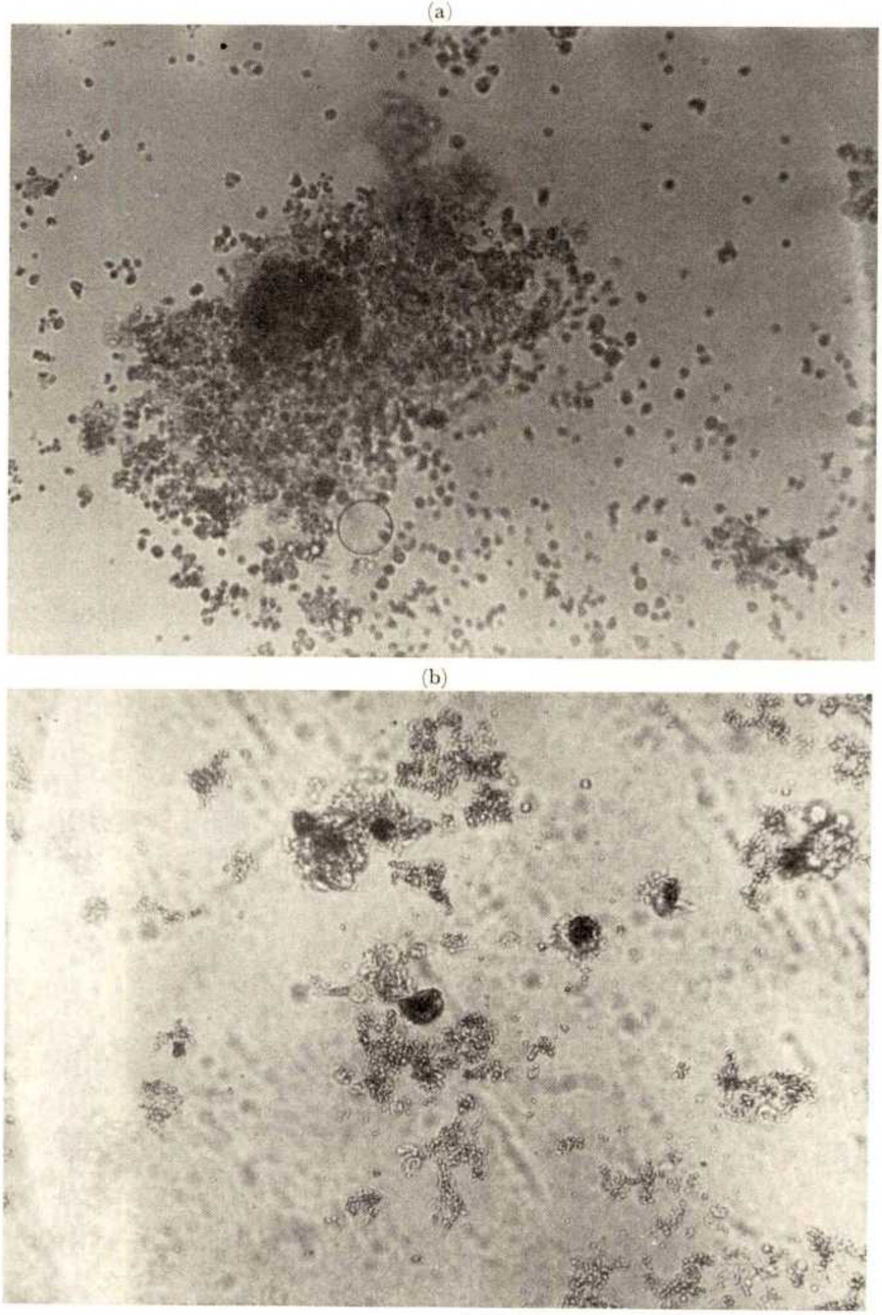

FIG. 2(*a* and *b*) *Phase-contrast photomicrograph showing complement-dependent cytotoxicity of autologous serum; only a few cells and cellular debris remain attached to the cover glass.* *a* × 132; *b* × 285

other hand, are probably eliminated by the humoral antibodies. Thus, a constant battle goes on between the tumour and host defences and a quantitative factor perhaps controls the ultimate outcome (Hellström and Hellström, 1967).

Although cellular immunity appears to be deficient in advanced cancers, perhaps

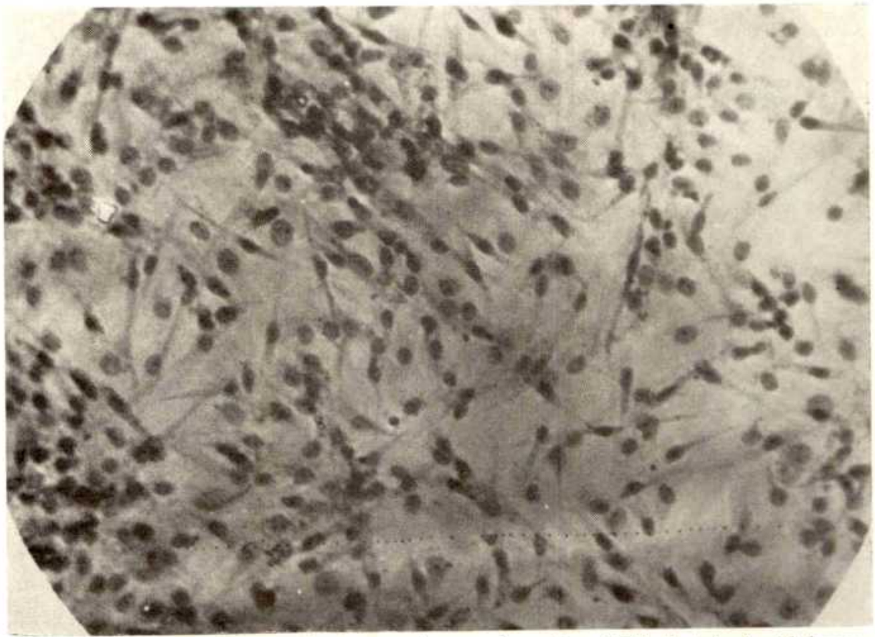

FIG. 3 *Cultured melanoma cells in normal serum from Case MM II stained with haematoxylin and eosin.* ×132

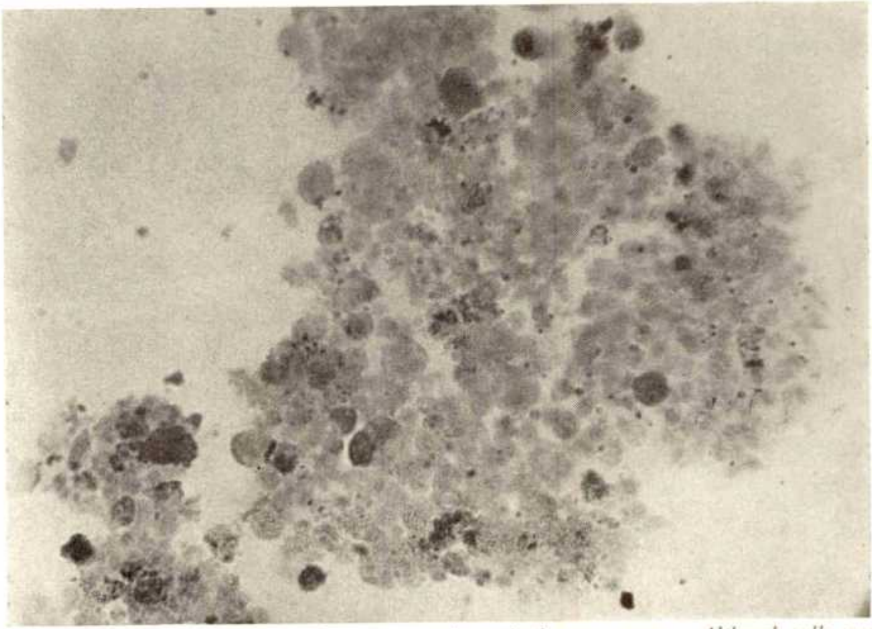

FIG. 4 *Melanoma cells from the same case in patient's own serum. Although cells are attached to the cover glass they show extensive nuclear and cytoplasmic degeneration. Haematoxylin and eosin.* ×285

because of general debility and immune exhaustion by constant bombardment with tumour antigens (Green, Anthony, and Baldwin, 1967), it plays an important role in host resistance to tumours (Law, 1969). Hughes and Lytton (1964) and Stewart (1969)

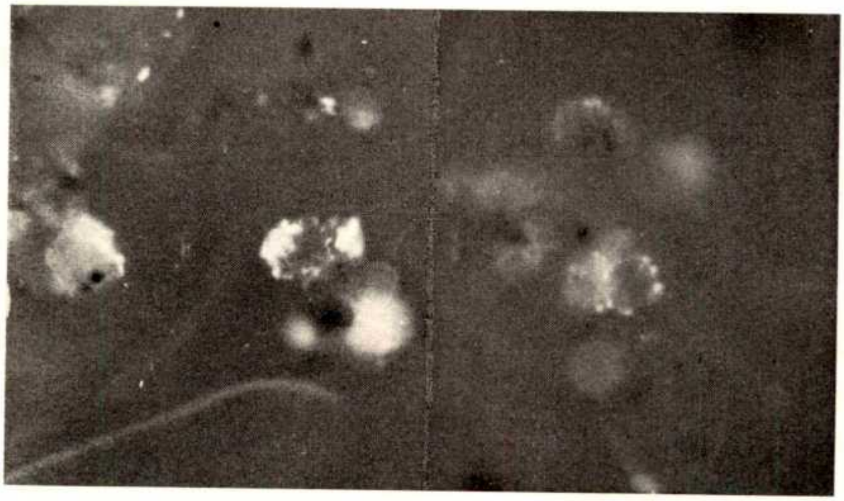

FIG. 5 *Membrane and cytoplasmic fluorescence of melanoma cells treated with autologous serum.* ×380

Table I *Clinical, pathological, and serological data of uveal melanomas studied*

Tumours		*MM* 1	*MM* 2	*MM* 3	*MM* 4	*MM* 5	*MM* 6	*MM* 7	*MM* 8	*MM* 9	*MM* 10	*MM* 11	*MM* 12	*MM* 13	*MM* 14	*MM* 15	*MM* 16	*MM* 17	*MM* 18	*MM* 19	*MM* 20	*MM* 21
Age (yrs)		59	61	68	55	35	60	55	71	59	64	37	60	61	66	62	65	53	48	73	45	65
Sex		F	M	F	M	F	M	F	F	M	F	M	F	F	F	M	M	M	M	M	F	M
Site		C	C	C	C	C	C	C	C	C	C	C	C	C	C	I	C.B	C	C	C	C	C
Cell type		S	E	S	S	S	S	S	S	S	S	S	S	E	M	E	S	M	M	S	S	S
Reticulin content		M	H	M	H	H	H	L	M	L	L	M	H	M	H	H	L	H	H	M	M	M
Pigmentation		L	M	H	L	M	N	N	L	N	L	N	L	M	H	H	M	M	H	M	L	N
Necrosis		–	+	–	+	–	–	–	–	–	–	–	–	+	–	+	–	+	–	+	–	–
Cellular infiltration		–	+	–	–	–	–	+ . .	–	–	–	–	–	–	–	–	–	+	+	+	–	–
Cytotoxic test		– ?	– ?	– ?	+	–	–	+	+	–	–	+	–	+	–	–	+	+	–	–	–	–
RNA inhibition		o	o	o	(–x)	o	o	o	o	o	o	o	o	+	o	o	o	+	–	o	o	o
Immunofluorescence	AS	o	o	– ?	o	o	–	+	+	–	–	o	o	+	o	o	o	o	–	–	–	–
	HS	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

– = Negative/Absent
+ = Positive/Present
o = not tested
– ? = poor growth in all chambers
+ ? = shown to be positive when culture was stained

(–x) = quenching made the result unreliable so recorded as negative
AS = tested against patient's own serum
HS = tested against serum of other uveal melanoma patients

Site C = choroid
I = iris
CB = ciliary body

Cell type S = spindle
M = mixed
E = epithelioid

Reticulin pigment L = light M = moderate H = heavy N = none

found that a quarter of the patients with carcinomas and sarcomas gave delayed skin reactions in response to intradermal inoculation of autologous tumour cell extracts. A similar response has been recently demonstrated in about 40 per cent. cases of skin melanomas (Fass, Herberman, Ziegler, and Kiryabwire, 1970). A positive *in vitro* test for cellular immunity in melanoma has been reported by Hellström, Hellström, Pierce, and Yang (1968). Humoral antibody response to human and animal melanomas has been described in the past (Finney, Byers, and Wilson, 1960; Coon and Fain, 1960). But more conclusive evidence has been provided by Lewis and others (1969), who have not only confirmed the findings of Morton, Malmgren, Holmes, and Ketcham (1968) and Muna, Marcus, and Smart (1969), but have also shown that circulating antitumour antibodies are directly related to the clinical state, antibodies being absent in metastasizing melanomas.

One-third of the melanoma patients tested in our present series had in their sera cytotoxic antibodies which reacted with the cells of their own tumour in tissue culture. Immunofluorescence investigations have shown that antigen is found both on the surface and inside the tumour cells. Melanin is perhaps not one of the antigens because sera from patients with vitiligo containing antimelanin antibodies do not react with melanoma cells (Langhof, Feuerstein, and Schabinski, 1965). Although Lewis and others (1969) have demonstrated that antibodies reactive against cytoplasmic constituents of skin melanomas cross-react with melanoma cells of other individuals, we did not find similar cross-reactivity among the uveal melanomas and we are, therefore, in agreement with Mansell and Verrier-Jones (1971) that the antibodies in melanoma are perhaps individual-specific. Three of our cases, in which the tumour was treated with normal serum, showed fluorescence in a few cells. This was due either to the non-specific fixation of some of the isoantibodies present in the normal serum (Morton and others, 1968) or to *in vivo* fixation of autoantibodies on some of the tumour cells. Since uveal melanomas contain blood sinuses devoid of endothelium in which blood circulates quite freely among tumour cells (François, 1963), it is possible that some of the antibodies become fixed to the tumour cells. In fact this sort of fixation has been found in a large number of cases of skin melanomas (Mansell and Verrier-Jones, 1971) and the role of such antibodies has been the subject of a recent survey (Hellström, Sjögren, Warner, and Hellström, 1971). The cytotoxicity test used in the present study not only takes into account the capacity of the cells to stick to the glass surface as an indication of viability, but also their growth potential as modified by pretreatment with sera containing specific complement-fixing cytotoxic antibodies. When in doubt, the cells sticking to the glass surface were fixed and stained and the cytological details studied for evidence of cell damage. In one case cells in the antiserum chamber did not fall off the cover glass and, therefore, according to Lewis's criteria, the test would have been reported as negative. Staining of the cells, however, indicated that all the cells in that chamber had undergone a sort of coagulative necrosis, nuclear details were absent and the cytoplasm was deeply eosinophilic. Complement-dependent inhibition of the synthesis of RNA is a sensitive test which measures cytotoxicity. A reliable result requires a fairly high viability index of the original cell suspension. Heavily pigmented and necrotic tissues often present difficulty since they are likely to produce quenching, which makes the result unreliable.

Reese, Archila, Jones, and Cooper (1970) have recently published an analysis of 100 cases of uveal melanoma and have shown that 22 per cent. of cases had cellular and lytic necrosis of the tumour and 5 per cent. had coagulative necrosis. Flat malignant choroidal melanomas are particularly inclined to show necrosis and inflammatory changes, and Font, Spaulding, and Zimmerman (1968) found post-necrotic scarring in 40 per cent. of their cases. Uveitis is not uncommon in uveal melanomas and is generally believed to be the result of necrosis and release of cytotoxic agents. Uveitis, can, however develop in the absence of necrosis (Kirk and Petty, 1956) and, conversely, tumour necrosis from photocoagulation may not lead to inflammation (Hepler, Allen, and Straatsma, 1968), so that it is necessary to revise our ideas of the genesis of uveitis in intraocular melanoma. This may have an immunological basis such as has been postulated for the cellular infiltrates found in other malignant conditions. Even if tumour necrosis controls the ultimate severity of the inflammatory reaction, it cannot be explained, at least in some cases, only on the basis of hypotension in vascular sinusoids of the tumour and passive congestion, since the size of the tumour appears to be unrelated to the incidence of necrosis (Reese and others, 1970). These authors, therefore, argue that inflammation and necrosis may represent an immunological response which causes the tumour to regress. Since we have now demonstrated cytotoxic autoantibodies in one-third of our cases, it is possible that these predictions may be true. In fact we found necrosis in about half of our positive cases, which might have some significance, since only 20 per cent. cases among non-reactors showed necrosis. Autoimmune serological reactions to ocular melanoma were studied by Howard and Spalter (1966). Although fifteen sera were examined, they looked for antibodies against autologous tumour in only three cases. No antigen-antibody reactions were detected by gel diffusion, haemagglutination, and complement-fixation techniques. These authors were, however, successful in detecting, by complement-fixation tests, specific antibody in rabbits immunized against uveal melanoma. Thus, in spite of their failure in a very small series to detect tumour antibody, they seem to conform to the idea that uveal melanomas are antigenic. They might have been successful if they had used immunofluorescence and tissue culture techniques and, therefore, they rightly conclude that "it would be of interest in future investigations of this type to include laboratory techniques for study of autoimmune phenomena on a cellular level".

Cellular immunity to uveal melanoma was studied in six female patients by exposing cell cultures to autochthonous lymphocytes and a negative result was reported (Hart, Reznikov, and Hughes, 1968). The authors mentioned various reasons why their finding should not be accepted as proof that no such response exists. Apart from their own remarks on failure to detect a cell-mediated immune response, there are a few more points worth consideration. Since these authors used trypsin to prepare their cell suspensions, it is likely that some of the antigens on the cell membrane (against which lymphocytes react) were removed during this process. After primary cultures were established, cells were subcultured, again using trypsin. Cytotoxicity tests were performed with cells obtained from such sub-cultures. It may be recalled that *in vitro* or *in vivo* cytotoxicity depends upon antigen density on the tumour cell membrane (Kaliss, 1962). In sub-cultures such density is likely to be low, because mitosis leads to dilution of antigen in descendant cells while mutant cells may not contain antigen at all, the total effect being loss of tissue specific antigen in culture (Weiler, 1959). We, therefore, believe that the reasons for their failure to detect cell immunity are twofold: first, they studied a very limited number of cases (6), and secondly they were dealing with cell suspensions of low antigenicity because of trypsinization and subsequent loss in sub-culture. Furthermore, it is also possible that their cases lacked cellular immunity either because of immune paralysis by direct inhibition and exhaustion (Dresser and Mitchison, 1968) or because of immune deviation (Asherson and Stone, 1965) or feed-back inhibition of the response by humoral antibodies (Axelrad and Rowley, 1968). It is also possible that sensitized cells migrated into the tumour so that very few were left in the general circulation (Lehner, 1970). It has recently been stated that cellular sensitization on the whole is quite uncommon in skin melanomas (Currie, Lejeune, and Fairley, 1971) and may be absent when the tumour is apparent (Nagel, Piessens, Stilmant, and Lejeune, 1971).

It is difficult to assign any definite role to the complement-dependent cytotoxic antibodies found in intraocular melanomas. As Lewis and others (1969) have suggested, their presence in skin melanomas might determine the clinical status of the patients, *i.e.* the cytotoxic antibody, being able to destroy blood-borne melanoma cells, may limit dissemination of the tumour and subsequent development of secondaries. This might be true with uveal melanoma also, wherein secondaries may be long deferred even in cases in which embolization into the general circulation has occurred early (Goder and Velhagen, 1970). A similar situation has been encountered in rats with primary fibrosarcomas which do not give rise to blood-borne metastases until antibody has been removed (Alexander and Hall, 1970). It must, however, be emphasized that more work is required to discover the role of tumour-specific antibodies in human uveal melanomas; a close follow-up of cases showing such response might provide some clue for further studies. Patients showing specific antibody response are being followed up and the result will be communicated in due course.

Summary

Tumour tissue and sera were obtained from 21 cases (10 females and 11 males) of uveal melanoma. Autoantibodies reactive against the patients' own melanoma cells (autochthonous antigen) were demonstrated in seven cases by complement-dependent cytotoxicity in short-term culture, complement-dependent inhibition of RNA synthesis, and immunofluorescence staining of viable and fixed tumour cells in histological preparations. Although the presence of antibodies in serum could not be correlated with cell type, reticulin content, and pigment distribution, tumour necrosis was evident in half of the positive cases. No cross-reacting antibodies were demonstrated. The relevant literature on the nature and role of immune reactions in human neoplasms in general and in melanomas in particular has been reviewed and the possible role of the autoantibodies demonstrated in the present study has been suggested. Further study and close follow-up are necessary before any definite conclusions can be reached.

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Vascular system of the optic nerve head and retina in the pig

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Several investigators have recently used the pig (*Suidae*) as an experimental model in the study of the retinal vasculature (Ashton, Dollery, Henkind, Hill, Paterson, Ramalho, and Shakib, 1966; Dollery, Henkind, Paterson, Ramalho, and Hill, 1965; Dollery, Henkind, Kohner, and Paterson, 1968; Kohner, Dollery, Henkind, Paterson, and Ramalho, 1967; Kohner, Dollery, Shakib, Henkind, Paterson, de Oliveira, and Bulpitt, 1970; Henkind and Dollery, 1966). The retinal circulation in the pig is holangiotic and is said to resemble closely that of man (Bloodworth, Gutgesell, and Engerman, 1965; Duke-Elder, 1958; Langenbacher, 1880). Most of the literature available on this subject either concerns a single aspect of the microcirculation or is confusing. It was felt that a reinvestigation of the retinal vasculature system would be of interest to experimentalists using the pig as a laboratory animal.

It is important at the outset to understand the origin of the orbital blood supply in the pig. As is common in the lower mammalia, the major orbital supply is derived from the external carotid circulation *via* the external ophthalmic artery (Duke-Elder, 1958; Prince, Diesem, Eglitis, and Ruskell, 1960). The internal carotid is almost vestigial and the cerebral circulation, arising from a carotid rete derived from the ascending pharyngeal artery, makes a minor contribution *via* the internal ophthalmic artery (Daniel, Dawes, and Pritchard, 1953). The retinal arteries arise from the main ciliary vessels and pierce the sclera around the optic nerve head. Retinal veins come out through scleral channels to join the posterior ciliary veins (Prince and others, 1960).

Materials and methods

The retinae examined were obtained from seven pigs in their first week of life and two at 3 months of age. Direct ophthalmoscopy was carried out under phenobarbital anaesthesia with complete mydriasis. Animals were injected with Indian ink by either the intraventricular or the intracarotid route as described by Ashton, Ward, and Serpell (1954) and Ashton and others (1966). Upon immediate enucleation the eyes were placed in 10 per cent. formol saline, and fixed for 24 hours. The anterior segment was removed and the vessels were examined *in situ* by means of a binocular dissecting microscope. Globes were oriented with pre-placed superior limbal sutures. After extirpation of the vitreous the retinae and remaining parts of the ciliary bodies were dissected free of the choroid and sclera. The retinae were incised radially, laid flat on glass slides, and gently mounted in warm 30 per cent. glycerin. One retina, after examination and photography, was cut by hand into thin sections which were laid on their sides and examined. Several eyes, sectioned equatorially, bleached with potassium permanganate and oxalic acid, and cleared with glycerin, were examined *in situ* and after removal of the scleral coat. Globes from two animals were embedded in paraffin for histological study. Sections were stained with haematoxylin and eosin, with PTAH, and by silver impregnation for nerve fibres. Several retinae were digested by the pepsin trypsin technique (Ashton, 1963) and stained with PAS and haematoxylin.

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Results

In vivo OBSERVATION

The fundus of the pig lacks a tapetum (Lindsay Johnson, 1901; Prince and others, 1960), and its colour varies from red-brown to grey, depending upon the amount of pigmentation. Three or four major arteries and several smaller vessels arise from the periphery of the inferiorly placed oval disc, the accompanying veins draining more centrally. Arteries emanating from the papilla as isolated channels often bifurcate near the disc while some veins are seen to anastomose close to the disc margin (Fig. 1). The normal arteriovenous ratio is three to two. The vascular pattern is as described by Bruns (1882) with superior and inferior temporal and nasal vessels. By direct ophthalmoscopy and in photographs in the literature (Ashton and others, 1966), the major vessels are seen to cast a shadow on the retinal surface and hence appear to lie superficially (Fig. 2). In contrast to previous reports (François and Neetens, 1962; Michaelson, 1954; Prince and others, 1960), the present study indicates that at crossings veins generally lie over the arteries, although the opposite also occurs. Arterial and venous branching is both dichotomous and bisular (side arm), the latter prevailing on the arterial side. An area corresponding to a macula is not noted on ophthalmoscopy.

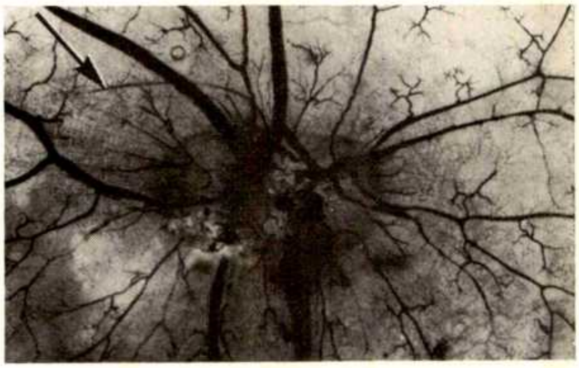

FIG. 1 *Pig. 2 Indian ink injection of disc and peripapillary area. Note bifurcatoin of arterial channels and anastomosis of venous channels near disc. Bisular branching of arterioles is evident as is the hyaloid artery (arrow).* ×13

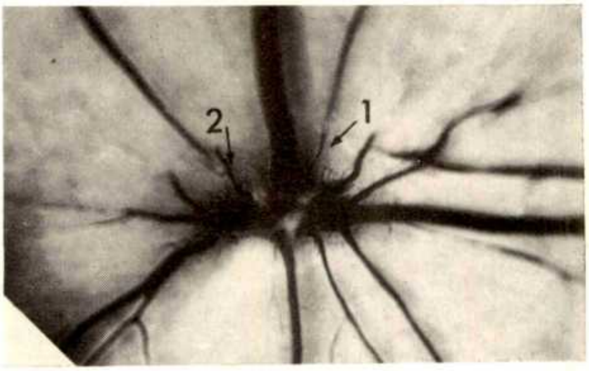

FIG. 2 *Pig 5a. Indian ink infection of optic disc area photographed* in situ. *Note smaller venous channels draining into large vessels (arrows 1 and 2) of nerve head. Larger vessels cast a shadow upon the retina.* ×13

HISTOLOGICAL AND THIN SPECIMENS

The retinal vessels are seen to penetrate the sclera about the optic nerve with the occasional vessel branching at the disc to enter the choroid and the retina. There is no central retinal artery, and fine capillaries are evident within the optic nerve head overlying the lamina cribrosa. The larger vessels lie close to the internal limiting membrane bulging into the vitreous; however, as suggested by Bruns (1882) and Bloodworth and others (1965), they are truly within the nerve fibre layer (Fig. 3). A single adventitial coat is noted at arterio-venous crossings.

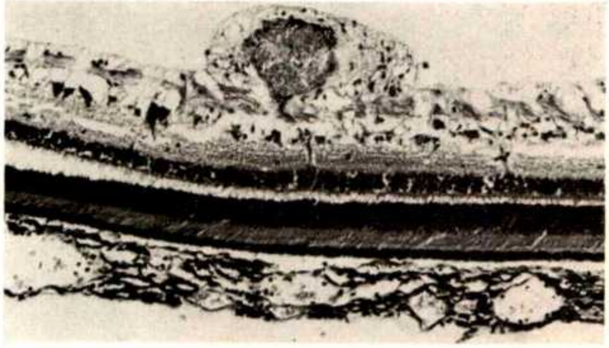

FIG. 3 *Pig. 9 Larger vessel lying close to internal limiting membrane and bulging into vitreous. Haematoxylin and eosin.* ×115

In the immediate peripapillary area, four capillary layers are noted (Fig. 4):

(*a*) Superficially within the nerve fibre layer;
(*b*) In the ganglion cell layer;
(*c*) In the middle of the outer plexiform layer;
(*d*) At the union of the inner two-thirds and outer one-third of the inner molecular layer.

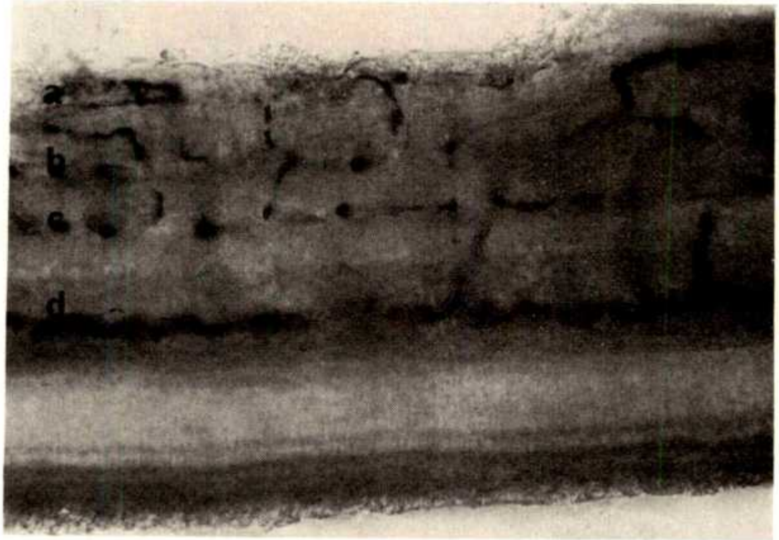

FIG. 4 *Pig 5. Immediate peripapillary area. Four capillary layers are evident (a, b, c, d). Indian ink injected thin sections viewed coronally.* ×308

This distribution differs somewhat in detail from that described by Bloodworth and others (1965). Towards the equatorial region only three distinct layers are evident, the most superficial having become attenuated (Fig. 5, opposite). Nearer the periphery the capillary nets tend to merge, particularly those within the ganglion cell and inner plexiform layers. Several sections showed a large thin-walled peripheral venous channel adjacent to the ora ciliaris retinae (Fig. 6, opposite).

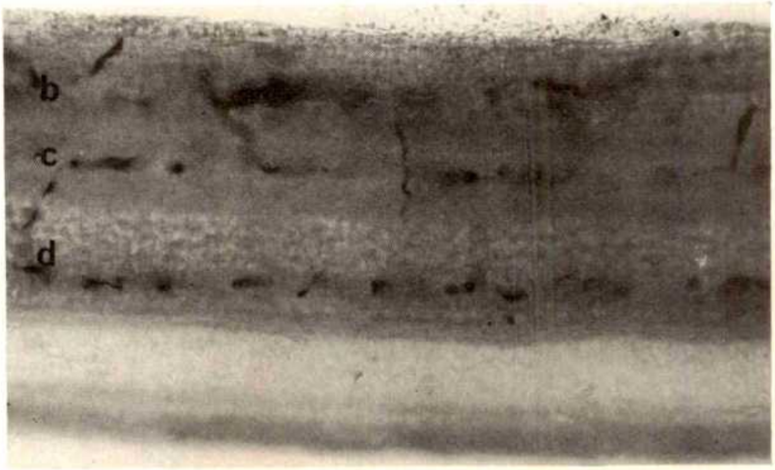

FIG. 5 *Pig 5. In the equatorial region only three layers are now distinct (b, c, d).* ×308

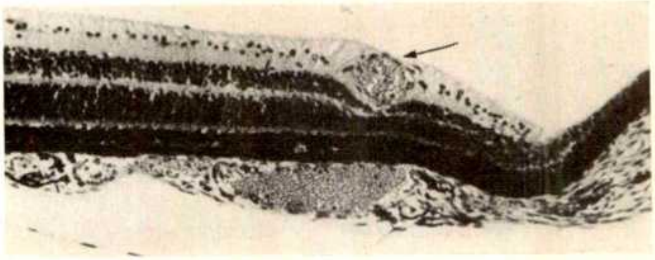

FIG. 6 *Pig 1. Thin-walled peripheral venous channel (arrow). Haematoxylin and eosin.* ×126

INJECTED SPECIMENS

In many of the young animals remnants of the hyaloid system are present at the disc and extend forward as a hyaloid artery to anastomose with a prominent tunica vasculosa lentis. The tunica is not present in the animals at 3 months of age.

DISC AND PERIPAPILLARY AREA

Specimens of the optic nerve head and surrounding sclera cleared by a modified Spalteholz technique show a distinct circle of Zinn-Haller previously noted by Bruns (1882) (Fig. 7).

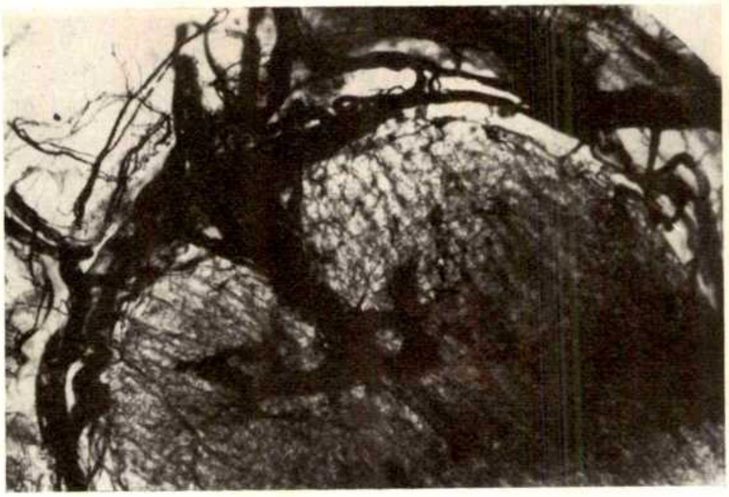

FIG. 7 *Pig 3. Left optic nerve head cleared by modified Spalteholz technique. Note distinct arterial circle of Zinn-Haller.* ×18

Vessels arising from the circle of Zinn-Haller are distributed in the following manner:

(1) As recurrent branches anastomosing with the rich plexus of vessels of the pial sheath;

(2) As branches anastomosing with the capillary nets of the lamina cribrosa and the retro- and pre-laminar nerve head;

(3) As some of the smaller vessels supplying the immediate peripapillary area.

The dense capillary nets supplying the nerve head and peripapillary zone arise from branches of the circle of Zinn-Haller as well as from separate smaller channels penetrating the sclera around the optic nerve head. These observations support the angiographic studies which have suggested that the blood supply of the optic disc and immediate area appears to be distinct from that of the surrounding retina (Dollery and others, 1968). Several specimens in which the peripapillary choroid is intact show an anastomosis of the vessels of the choroid with the capillary nets of the prelaminar optic nerve. The deeper peripapillary venous plexus drains either into small venous channels anastomosing at the disc with larger veins (Fig. 2) or is continuous with the prelaminar capillary plexus which in turn drains into major retinal veins. It should be noted that individual variation of blood supply exists and that the capillary nets of the retrolaminar and laminar as well as of the prelaminar optic nerve are continuous.

A distinctive radial peripapillary net, as described by Henkind (1967a, b), is most evident superiorly as well as nasally and temporally. This study supports observations made by Dollery and others (1968) that these capillaries are derived chiefly from intraretinal arterioles and only occasionally connect with vessels at the disc margin. They pursue a relatively long straight course undergoing repeated anastomoses with underlying arterioles (Fig. 8). Ultimately these vessels join the underlying capillary nets in the nerve fibre layer. This differs from the human counterpart wherein these vessels are said to anastomose directly with underlying venules (Henkind, 1967a). Injected specimens confirmed observations made *in vivo* with regard to vessel size, arterio-venous crossings, and type of branching.

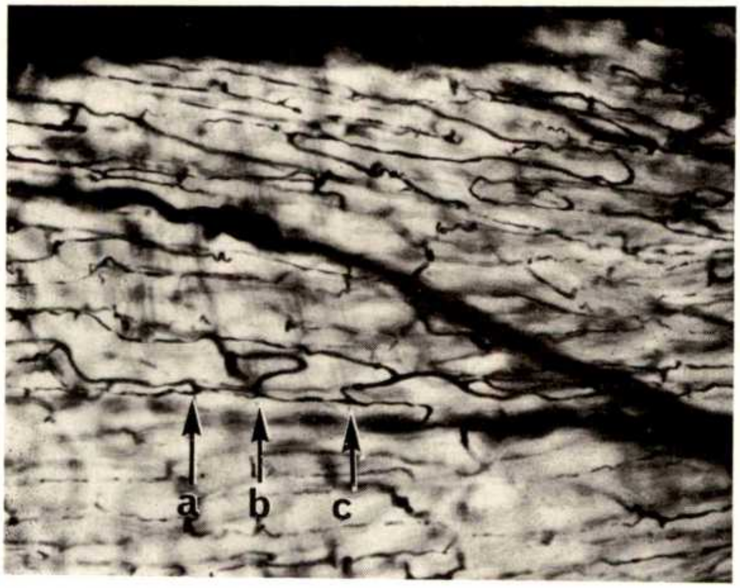

FIG. 8 *Pig 2. Radial peripapillary capillaries undergo repeated anastomoses with underlying arterioles (arrows a, b, c).* ×138

REMAINDER OF FUNDUS

Superimposition of territories of major arterial and venous channels is rare. An obvious feature, characteristic of a number of mammalia (Bruns, 1882; Prince and others, 1960), is the large venous channel that extends throughout the temporal periphery immediately adjacent to the ora ciliaris retinae (Fig. 9). These vessels arise from veins extending peripherally towards them and are seen to drain into the inferior nasal, inferior temporal, and (occasionally) into the superior temporal veins. Vein endings of this so called, "circulus venosus anterior" (Bruns, 1882) never anastomose directly but may do so through terminal capillary nets. The remainder of the periphery is supplied by loose-meshed capillary nets extending between both arterial and venous channels.

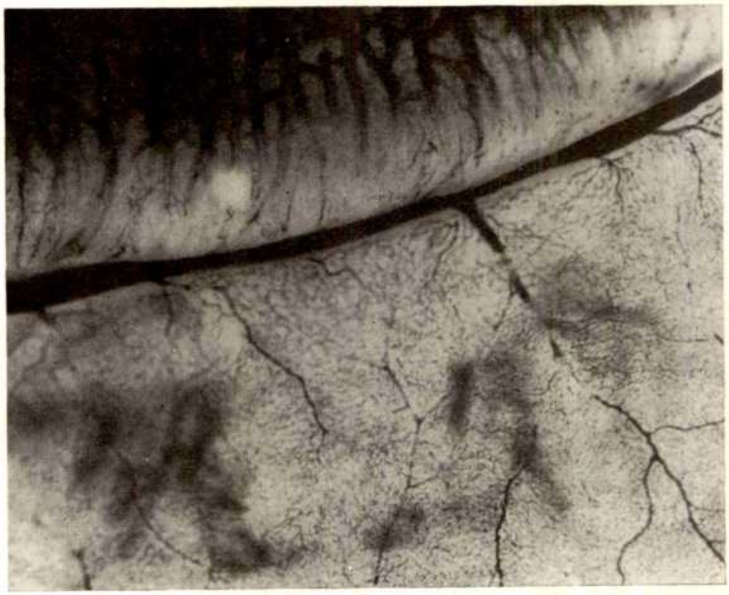

FIG. 9 *Pig 5a. Indian ink injection with pigmented ciliary epithelium bleached. The large peripheral venous channel is striking.* ×18

A specimen in which the pigment epithelium of the ciliary body had been removed revealed an unusual and, to our knowledge, unique observation. Occasional arteriolar and capillary size channels extend superficially across the ora ciliaris to lie on the ciliary body (Fig. 10). Bleached specimens confirmed this observation and indicated that such channels are rare, are seen only in the younger animals, and appear attenuated, often injecting incompletely. These channels have no connection with the ciliary circulation. Occasional islands of retinal tissue were also seen to extend on to the ciliary body, a feature noted commonly in man (Duke-Elder, 1964).

A capillary-free area suggesting macular function is not evident in our specimens. This finding is in accord with that noted by Bloodworth and others (1965) and is contrary to the suggestion by Prince and others (1960) that an area centralis exists supero-temporal to the disc. However, a broad zone, supplied by capillaries alone, extends across the horizontal axis of the retina (Fig. 11*a*). The only major vessels crossing this zone are those supplying and draining the superior sector. Coronal and sagittal serial sections through this zone and the remainder of the fundus show a general tendency to an increased ganglion cell population superior to the disc in this area, most clearly shown in specimens embedded in celloidin where structural relationships are maintained (Fig. 11*b*).

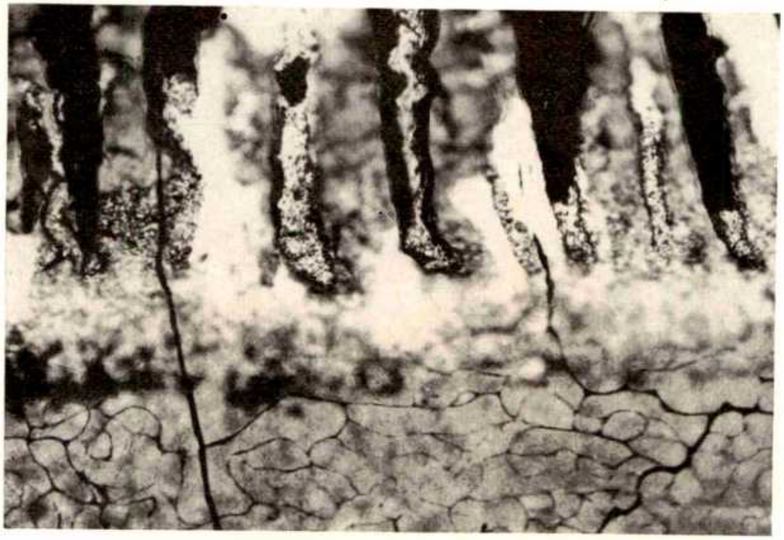

FIG. 10 *Pig 2 Vascular channels extending superficially across the ora ciliaris.* ×62

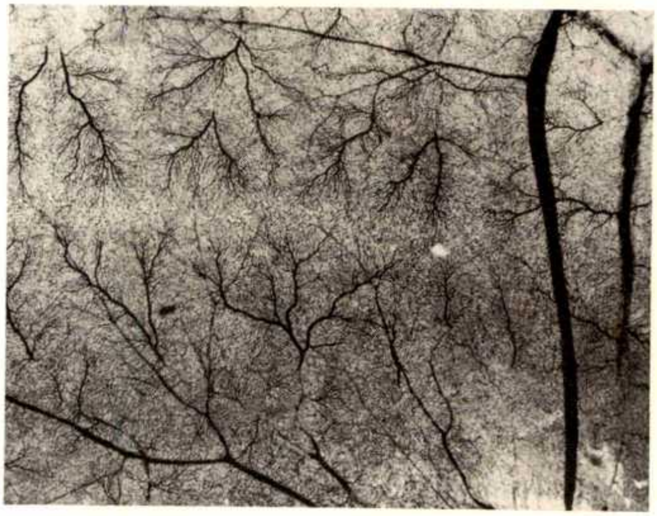

FIG. 11*a* *Pig 3. Broad zone supplied by capillaries alone extending horizontally across superior pole.* ×18

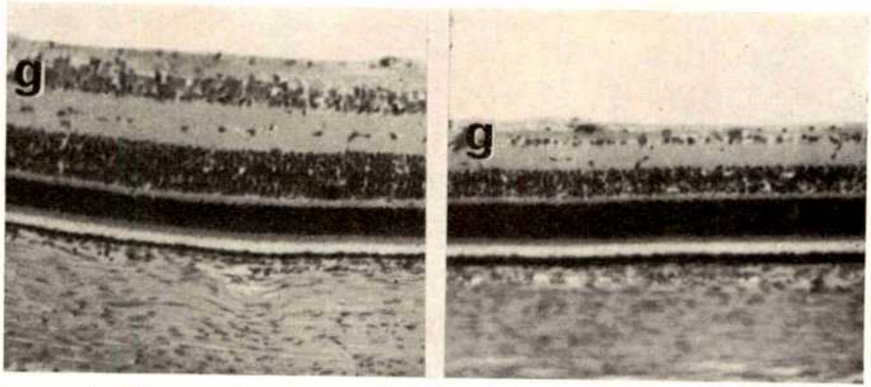

FIG. 11*b* *Pig* 1. *Sections of the retina demonstrating increased ganglion cell population* (*g*) *of the horizontal zone supplied by capillaries alone* (*left*), *compared to a zone equidistant below the disc* (*right*). *Celloidin embedded. Haematoxylin and eosin.* ×168

Schultze (1892) and Bloodworth and others (1965) have described a capillary-free zone about the arteries in the pig, while Henkind and de Oliveira (1967) have thrown some doubt on its existence. The present study supports the existence of such a zone, although it is less evident in the pig compared to other species. The reason for a less obvious capillary-free zone is two-fold.

(*a*) Since the major vessels lie very superficially within the retina (Fig. 3), often bulging into the vitreous, the zone exists only as a concavity beneath the vessel where it comes into relation with a capillary bed;

(*b*) Arteriolar channels arising from these major vessels are not only superficial and short but, by virtue of their size, have a narrow capillary-free zone.

Bruns (1882) was struck by the peculiar propensity for large venous channels to form deep within the inner molecular layer and to ascend rather abruptly to drain into major veins. He also suggested that the arterioles ramify chiefly within the ganglion cell and outer plexiform layers. In essence, this study is in accord with these observations. Several new findings, however, must be added. As the venous channels ascend, often in a stepwise fashion, they collect vessels from the capillary nets within each layer (Figs 12 and 13).

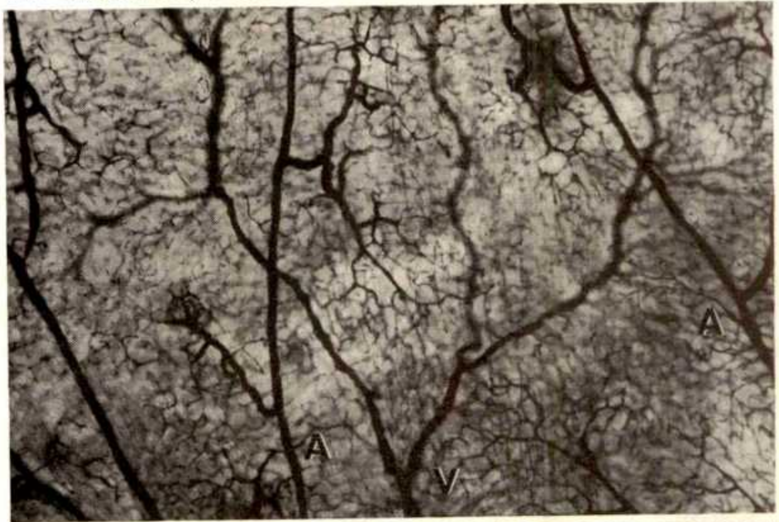

FIG. 12 *Pig 2 Venous channel (V) flanked by arterioles (A). Photographed in the superficial layers. Note arterioles and only part of venule in focus.* ×62

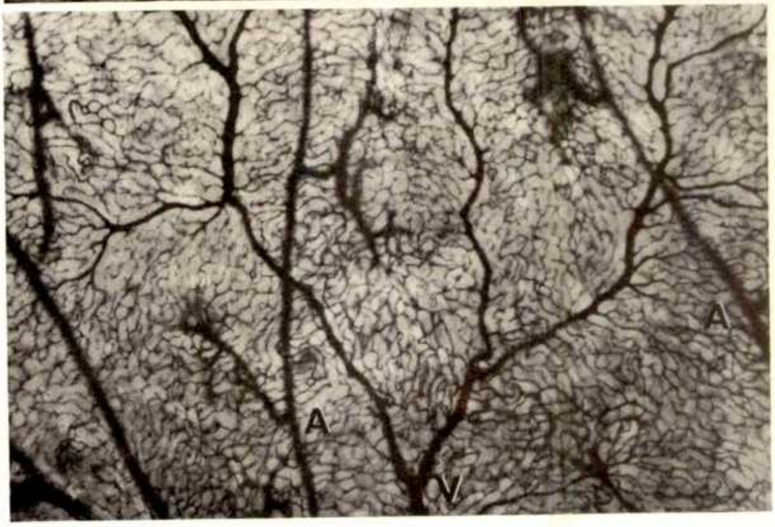

FIG. 13 *Pig 2. Same area as Fig. 12 photographed at level of venous layer. Note arterioles (A) are now out of focus.* ×62

For the most part the arterioles form capillary nets within the superficial layers and these, in turn, communicate with those in the inner molecular layer (Fig. 14). However, thin sections of the injected specimens viewed coronally revealed a number of vessels of arteriolar size that appear to connect with the capillary nets of all three layers (Fig. 15). This is not as obvious a feature as the communication of the venous channels within all layers. Fig. 16 (opposite) is an artist's drawing of a conceptual model of the circulation within the pig retina as outlined in this study.

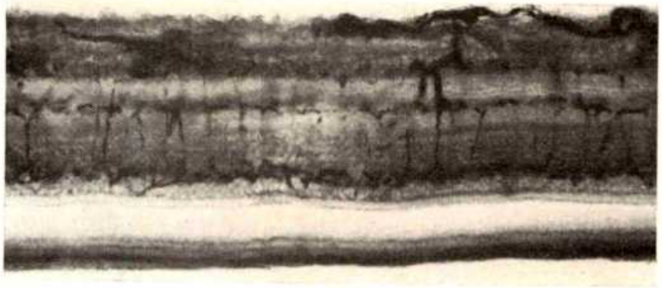

FIG. 14 *Pig 5. Indian ink injection viewed coronally. Note arterioles form capillary nets in superficial layers which in turn communicate with those in the inner molecular layer.* ×138

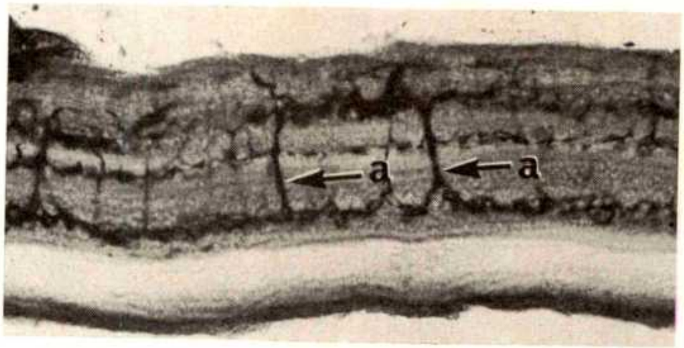

FIG. 15 *Pig 5. Note several arteriolar-sized channels (a) communicating with capillary nets of all three layers.* ×138

Bruns (1882) described the capillary network as rather narrow, polygonally arranged, and with a maximum net size of 33 μ and a minimum of 22 μ. In the present study capillary net size is measured from representative photographs at magnifications of 175 ×. Fields selected are in the plane of the intermediate and deeper capillary layers and midway between either arterial or venous channels. Measurements are taken in the horizontal and vertical axis at 4 mm. and 8 mm. from the centre of the papilla. The results are set out in the Table (p. 817).

Thus, the average mesh size in the intermediate net is 71 μ (range 17–154), while in the deeper layer the average mesh size is 48 μ (range 11–154). Generally, the mesh size in both the deeper and the intermediate layer tends to be greater as the retinal periphery is approached.

RETINAL DIGESTS

The vascular plexus in the digests appears to be particularly dense with the collapse and superimposition of capillary networks. Arterial elements are more cellular and stain more intensely than do veins. Capillaries are of uniform size and are lined by endothelial cells with pericytes incorporated in the vessel walls. In several areas capillary retraction is evident though not prominent. Although not a striking feature, PAS-positive material

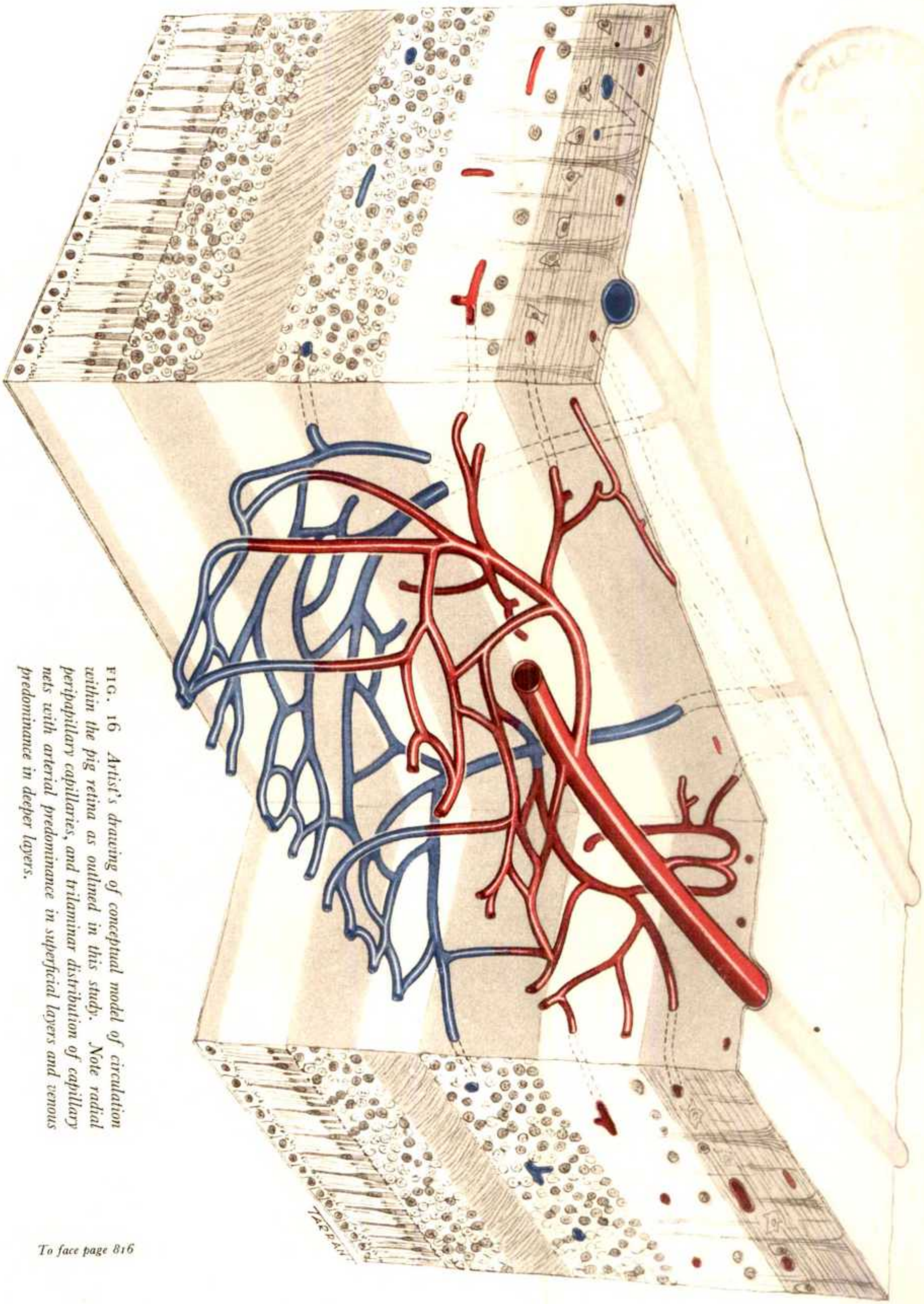

FIG. 16 *Artist's drawing of conceptual model of circulation within the pig retina as outlined in this study. Note radial peripapillary capillaries, and trilaminar distribution of capillary nets with arterial predominance in superficial layers and venous predominance in deeper layers.*

To face page 816

Table *Lengths and widths of capillary nets of the intermediate and deep vascular layers*

Layer		*Intermediate*				*Deep*			
		Length (μ)		*Width* (μ)		*Length* (μ)		*Width* (μ)	
		Average	*Range*	*Average*	*Range*	*Average*	*Range*	*Average*	*Range*
Area examined	4 mm. Nasal	120	81–171	42	29–51	64	45–80	29	23–40
	Temporal	91	71–144	34	29–45	54	45–80	25	17–29
	Superior	94	57–143	33	29–45	63	34–80	25	17–34
	Inferior	100	80–143	39	29–57	53	29–86	26	23–45
	8 mm. Nasal	116	109–154	30	17–40	83	29–114	35	23–45
	Temporal	119	97–137	31	23–40	94	40–154	23	11–29
	Superior	105	69–143	37	23–45	72	23–114	21	11–29
	Inferior	112	57–137	40	29–57	71	34–109	32	17–40

is present at the site of bisular branching of arterioles, particularly in the posterior pole. Henkind and de Oliveira (1968) previously noted this in the pig and considered it to be evidence of arteriolar annuli.

Discussion

Although the retinal circulation in the pig is holangiotic and bears some resemblance to that of man, several distinct differences exist:

(1) The orbital circulation takes origin from the external carotid system *via* the external ophthalmic artery which has a particularly long extraorbital course in this species (Prince and others, 1960). In contrast to the internal carotid circulation, this system is subject to major alterations in blood flow because it also supplies the head muscles (Keith, 1969).

(2) There is no central retinal artery and vein in pigs.

(3) The major retinal vessels lie very superficially in the nerve fibre layer in contrast to the deeper location in man. This distribution may reflect the origin of the retinal vascular system in the pig from the tunica vasculosa retinae (Schultze, 1892).

(4) An avascular foveal zone is not present in the pig.

(5) The capillary nets in the pig are distinctly trilaminar in distribution, except in the peripapillary zone where four layers are present. Evidence for this in both flat preparations and thin sections is striking. Human angioarchitecture is far less distinctly laminar; in fact, Toussaint, Kuwabara, and Cogan (1961) have suggested that the radial peripapillary plexus is the only truly bidimensional layer in the human retina.

(6) The capillary plexus in man had been said to be "suspended like a hammock between its feeding arterioles and draining venules" (Toussaint and others, 1961), with a greater density of nets on the venous side and frequent anastomoses between plexuses (Duke-Elder, 1961). By comparison, in the pig there is a striking association with either arterial or venous channels with less evidence of direct anastomoses between nets. The superficial vessels in the nerve fibre and outer plexiform layer are primarily arterial, whereas the deep net is chiefly venous in nature.

(7) The radial peripapillary plexus in the pig has a predominance of intra-arteriolar connections with few venular connections, in contrast to those noted in man (Henkind, 1967b).

(8) The presence of arteriolar annuli and large peripheral venous channels seen in the pig have not been noted in man.

The features which the human and pig retinal vasculature hold in common include:

(1) A periarterial capillary-free zone.

(2) Common adventitial coats at arterio-venous crossings.

(3) Similar capillary net size. In man the average capillary net size in the deeper layer is 50μ and in the superficial layer 80μ (Michaelson, 1954). In the pig comparable figures are 48μ and 71μ respectively. The capillary nets related to venules are denser and a general increase in net size, as the retinal periphery is approached, is noted in both man and pig.

(4) The retinal vessels are distributed in the strata between the inner limiting membrane and the inner nuclear layer in both man and pig.

(5) Retinal digests reveal many features shared by both man and pig. Study of the optic nerve head points to some similarities between the two circulations. The laminar region appears to be supplied by vessels arising from the circle of Zinn-Haller and from branches of the posterior ciliary arteries.

In the prelaminar region, vessels derived from the choroid and laminar branches make a contribution to the blood supply much as noted by Hayreh (1969) and Hayreh and Perkins (1969) in humans. In the pig the capillaries in the surface layer arise from smaller vessels at the disc margin originating from the prelaminar retinal vessels or from the circle of Zinn-Haller rather than recurrent branches from circumpapillary vessels as in humans (Hayreh, 1969; Hayreh and Perkins, 1969). The studies of Dollery and others (1968) have also suggested the blood supply of the optic nerve head in this species is distinct from that of the surrounding fundus, a finding paralleled in the human and primate nerve head (Hayreh, 1969; Hayreh and Perkins, 1969). The absence of the central retinal artery and vein, the extracranial origin of the ocular supply, and the consistent presence of a circle of Zinn-Haller are important differences between man and pig, thus the analogy cannot be carried too far.

A streak macula suggested in this study is a feature common to ungulates, the species to which the pig belongs (Duke-Elder, 1958). This feature is elegantly demonstrated in the ox eye studied by Priestley Smith (1921). The unusual and infrequent presence of vessels extending across from the retina on to the ciliary body or into the vitreous is more difficult to explain. Perhaps these vessels represent an anatomical variation or could be remnants meant to supply a retinal island on the ciliary body. They certainly appear to be embryological in origin and to be undergoing regression. Schultze (1892) described vessels in the periphery of the vitreous as well as a closely adjacent tunica vasculosa retina, but stated that no connections exist between the two. A reinvestigation of the development of the retinal vascular system in this animal might clarify the origin of these vessels.

Summary

In the pig there is no central retinal artery and major vessels lie superficially within the retina. There is a distinct radial peripapillary plexus and peripheral venous channels. Capillary nets within the retina are trilaminar with the superficial nets having chiefly arterial and the deep net venous associations. The blood supply of the optic nerve head and immediately surrounding retina have distinctive features described herein. Additional findings include a possible streak macula and vessels extending from the retina on to the ciliary body. The circulation of the optic nerve head and retina is compared to that of the human.

It is a pleasure to acknowledge the kind guidance and constant enthusiasm of Prof. Norman Ashton, F.R.S., who suggested this project. I should also like to thank Miss E. Robins and Messrs. G. Knight and A. McNeil for their technical assistance. I am grateful to Mr. Tarrant for his beautiful drawing and to Mr. Roger Keeble for his photographic help. Miss K. O'Malley's secretarial help is greatly appreciated.

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Early signs of the glaucomatous disc

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In a survey of new glaucoma clinic patients over 40 years of age, which was carried out in 1968 and was based on the appearance of the optic disc (Primrose, 1969), it early became clear to me that the peripapillary halo or ring, commonly considered to be more a senile than a glaucomatous condition, was in fact more than twice as likely to be associated with chronic simple glaucoma as not (Table) and that it occurred at an early stage of the disease.

Table *Glaucoma simplex and peripapillary atrophy*

New attendances in 1968			3,072
Cases selected for analysis on basis of appearance of disc			69
Glaucoma	Typical halo glaucomatosus	28	52
	Some juxtapapillary atrophy	21	
	Cupping without juxtapapillary signs	3	
Peripapillary halo	Glaucoma	28	43
	No glaucoma	10	
	Glaucoma suspects	5	
Other glaucoma suspects with some juxtapapillary signs			2

Some second eyes, which were still free of cupping, showed a halo similar to that seen in the first eyes. Only four of 28 cases of glaucoma with typical peripapillary haloes could be considered advanced. More than half the new cases of glaucoma showed a typical halo (Fig. 1, opposite), and this proportion excluded cases of chronic narrow-angle glaucoma in which the halo also occurs and cases of myopic peripapillary atrophy in which a susceptibility of the disc to the insidious development of cupping is already accepted.

Most of the remainder of the cases of glaucoma simplex showed a small amount of juxtapapillary choroidal atrophy, and only three out of 52 cases (*i.e.* 6 per cent.) showed no juxtapapillary signs. This is seen as a slight recession of the choroid away from the edge of the disc; it may be present only around one sector of the disc or may extend all round it as a narrow ring (Fig. 2, opposite, and Fig. 3, overleaf). This narrow zone of atrophy merges with the edge of the disc, but one can see that there is a thickness to the edge between the angulation of the vessels and the normal retina and choroid. I have been unable to find a specific description of this edging in the literature though many photographs and some paintings show it well (*e.g.* Fig. 551: Ballantyne and Michaelson, 1962).

These juxtapapillary signs, whether as a sector, a narrow ring, or a typical halo, are thought to arise from insufficiency in the zone of supply of one or more of the two or three

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short ciliary arteries which form, or fail to form, the circle of Zinn. The peripapillary choroid and prelaminar tissue of the disc is subject to the intraocular pressure, and because there are branches to the pial plexus the blood can take that alternative path when there

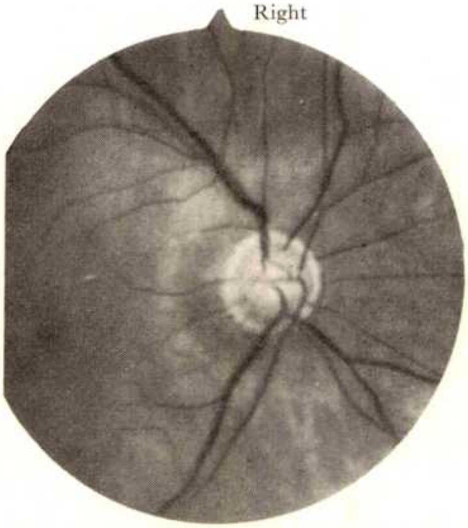


FIG. 1 *A woman aged* 65 *yrs in May,* 1968. *Right and left fundus photographs, showing typical peripapillary haloes. Right cup reaches edge of disc in upper temporal quadrant only. Early inferior arcuate scotoma and enlarged blind spot. Left cupping and pallor of upper half of disc. Considerable inferior field loss and enlarged blind spot. Intraocular pressure at first attendance:* 44 *mm.Hg* (*Schiötz*) *in the right eye and* 47 *mm.Hg in the left*

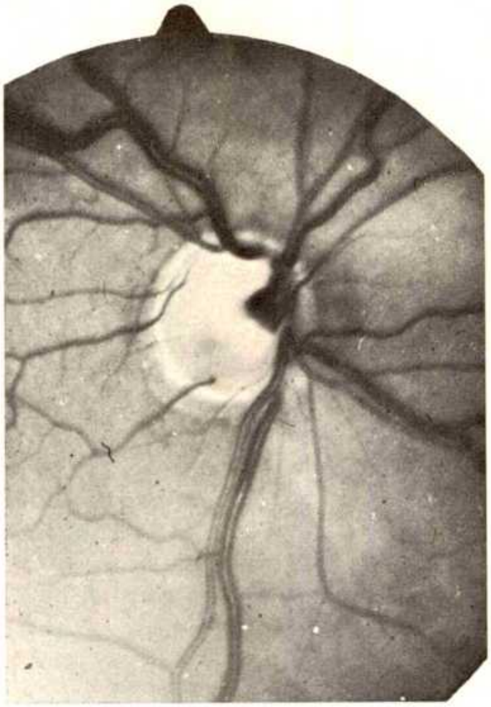


FIG. 2. *A man aged* 64 *yrs. The right fundus shows typical glaucomatous cupping, with vessels displaced to nasal side with angulation over edge of disc. Narrow juxtapapillary choroidal atrophy is present, probably all the way round, though most marked in inferior temporal section. Veins mildly congested. Marked inferior field loss. Intraocular pressure* 42 *mm.Hg* (*Schiötz*) *both eyes* (*Primrose,* 1969)

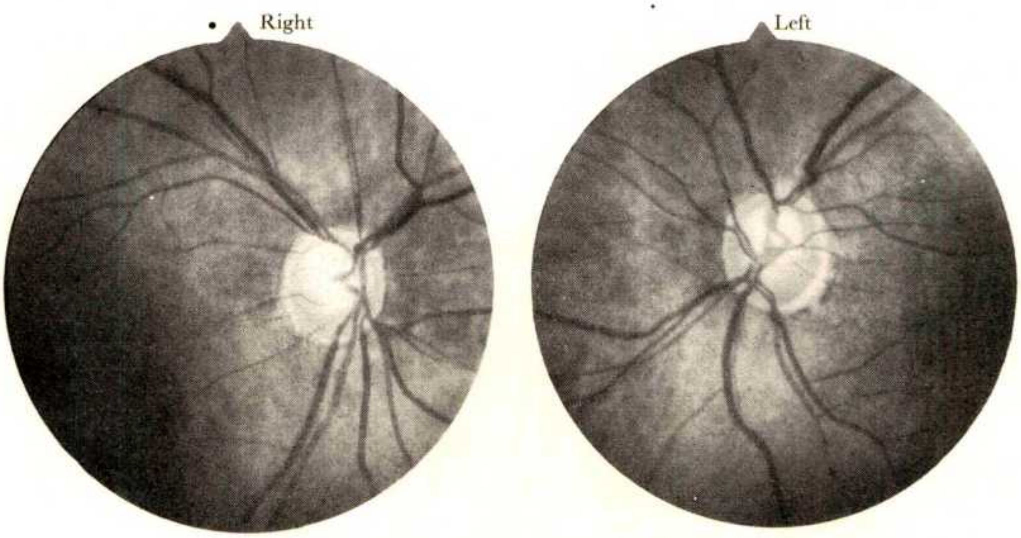


FIG. 3 *A woman aged 62 yrs with glaucoma simplex. In January, 1970, the right fundus shows glaucomatous cupping with very narrow peripapillary halo. The left shows a sharp inferior edge but the colour of the disc tissue is still good, with a sector of narrow juxtapapillary atrophy round the temporal half. The intraocular pressure at the first attendance was 40 mm.Hg (Schiötz) in both eyes. During the following year an increase in cupping occurred*

is increased pressure on these tissues, an alternative which is denied to the retinal artery system and the other posterior ciliary arteries (Gafner and Goldmann, 1955). Of several reports on fluorescein studies in glaucoma, Hayreh and Walker (1967) describe the general faintness of the disc and the failure of the peripapillary halo to fluoresce; Hayreh (1969) has shown that the peripapillary choroid is susceptible to raised intraocular pressure in the same way as the prelaminar tissue of the disc; and Boyd and Rosen (1970) have demonstrated a circumpapillary choroidal perfusion delay in cases of chronic glaucoma.

Sector haemorrhage at the edge of a glaucomatous disc has recently been described by Drance and Begg (1970). A perusal of the case notes made at the time of the first visit of the patients included in the 1968 survey, showed that three of the cases of glaucoma simplex had been recorded as having tiny haemorrhages on one disc such as Drance and Begg describe, and this observation was made without a specific search. More significantly, one of the suspects, who was kept under 3-monthly observation because of wide physiological cups and tensions between 17 and 27 mm.Hg (Schiötz) without any scotoma found on ordinary search on the Bjerrum screen, suddenly presented 2 years later with a tiny haemorrhage on the edge of the right disc (Fig. 4), obvious glaucomatous changes in both discs with slight marginal choroidal recession, and recently developed scotoma (Fig. 5). Also, two of the three who had originally shown haemorrhage on one disc subsequently developed a tiny haemorrhage on the other disc with an apparent increase of scotoma in one and of cupping in both. In these two cases the ocular tension was well controlled. One was considered to be a low-tension type and in both cases vascular insufficiency was thought to be the major defect. It appears to me that these haemorrhages, when they do occur, indicate a definite deterioration from an extra nerve fibre bundle succumbing to ischaemia.

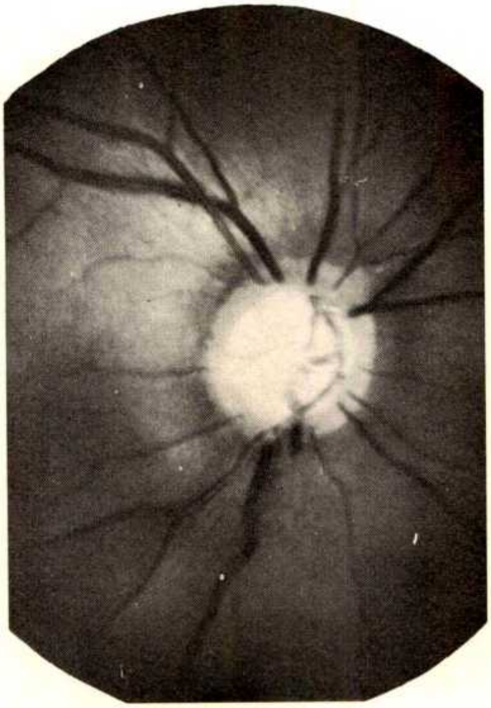


FIG. 4. *A woman aged 56 yrs with glaucoma simplex had been under observation for 2 years because of wide physiological cupping. In August,* 1970, *a small sector haemorrhage appeared at the lower edge of the right disc and the left disc had also become glaucomatous. The intraocular pressure did not rise above* 27 *mm.Hg in each eye even under provocation*

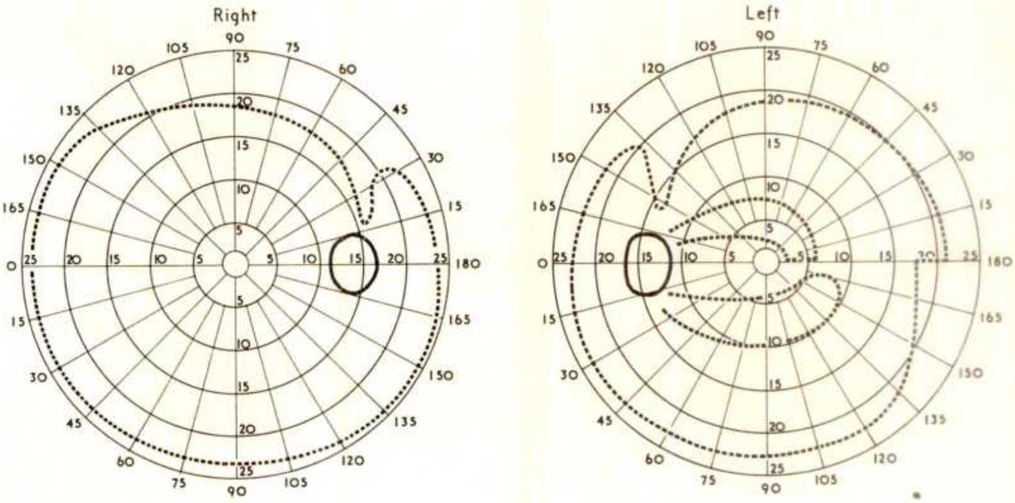
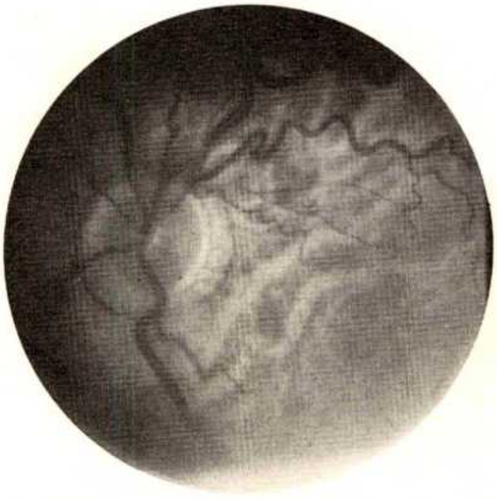


FIG. 5 *Visual fields of same patient as Fig.* 4, *showing an early glaucomatous scotomata in the right eye and typical glaucomatous scotomata in the left.* 10/2000 *and* 2/2000 *white*

One feature, seen more often in narrow-angle and secondary glaucoma (Figs 6 and 7, overleaf) than in chronic simple glaucoma, is dilation of retinal vessels. There is, as shown by Dobree (1956), a reaction to a raised pressure, usually to a considerable rise, which seems to be more marked in the veins. Once the disc has become atrophic, this reactionary vasodilatation is probably not operative, as an autoregulatory mechanism such as pertains

(6)



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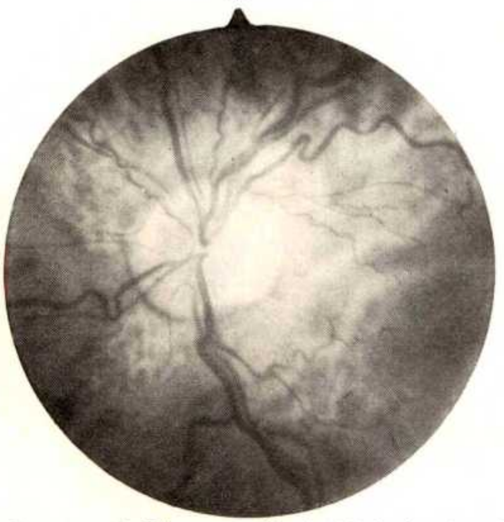


FIG. 6 *A man aged 58 yrs with subacute narrow-angle glaucoma. In February, 1968, the left fundus showed gross congestion of retinal veins, a reddened disc but no oedema, and slight peripapillary atrophy. There was an 18-mth history of "misty" attacks. When the photograph was taken the intraocular pressure was 69 mm.Hg (Schiötz)*

FIG. 7 *Left fundus (of same patient as in Fig. 6) in September, 1970, after the ocular tension had been normalized by a drainage operation 1 year previously. All congestion has gone but there are residual peripapillary changes*

to the retina would be dependent on active metabolism. Also, the rise in pressure seen in the vasodilated case is seldom reached in glaucoma simplex. With chronicity, permanently dilated loops may remain around the edge of the disc (Figs 8 and 9), even when all congestion has subsided with normalization of tension or the onset of atrophy. These dilated loops may sometimes, of course, be anastomotic, overcoming some element of venous thrombosis with which glaucoma simplex may sometimes be associated.

Summary

The incidence is given of glaucoma simplex discovered by routine examination of the optic discs of all new patients over 40 years of age for the year 1968.

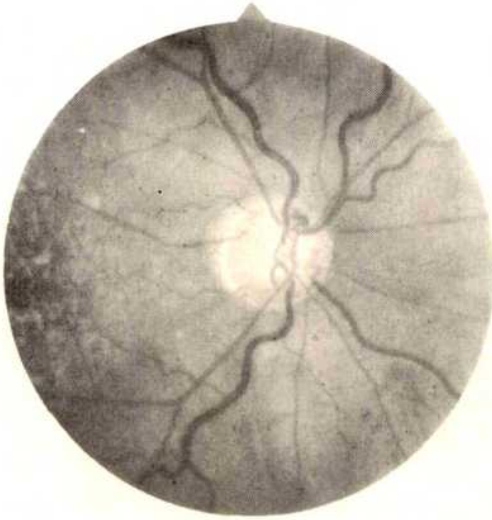
The peripapillary halo was present in more than half, often quite early in the disease, and was also present in many fellow eyes as yet free from cupping.

Most of the remaining cases showed sectors of choroidal atrophy merging with the edge of the disc, and only three out of 52 cases showed no juxtapapillary signs. This choroidal atrophy is thought to be another manifestation of the susceptibility of the intraocular tissues supplied by the circle of Zinn to raised intraocular pressure (the other susceptible tissue being that of the disc itself).

Sector haemorrhage was seen in three cases at their initial assessment and in one further case (watched for 2 years with suspicious discs) wherein it coincided with the development of glaucomatous change.

Dilated retinal veins, thought to be an autoregulative reaction to high pressure, and venous loops on the disc without any definite sign of thrombosis, are also described in cases of glaucoma of various types.

(8)



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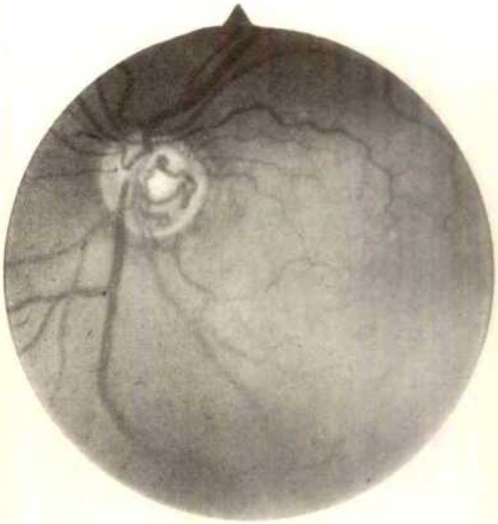

FIG. 8 *A man aged* 74 *yrs with pigmentary glaucoma. In November,* 1970, *the right fundus showed congested veins with venous looping at nasal edge and moderate glaucomatous cupping with narrow sector of edging on temporal side. Intraocular pressure,* 36 *mm.Hg (Schiötz) in the right eye and* 24 *mm.Hg in the left, subsequently rose to* 39 *mm.Hg in both eyes. Trephine operations were performed in February,* 1971

FIG. 9 *A man aged* 72 *years with glaucoma simplex. In August,* 1969, *the left fundus showed congested veins with extensive venous looping at the base of a moderate glaucomatous cup. There was no sign of thrombosis. The right eye also showed congested veins but no loops. The intraocular pressure was* 36 *mm.Hg (Schiötz) in the right eye and* 31 *mm.Hg in the left*

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Brit. J. Ophthal. (1971) **55**, 826

Urokinase in the management of traumatic hyphaema

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There is no general agreement in the literature on the correct management of traumatic hyphaema*—even about such minor points as whether to pad the injured eye only or to pad both eyes, and whether to use a miotic or mydriatic or not. It was therefore decided in 1966 to treat a controlled series of cases of traumatic hyphaema with various preselected regimes. This prospective study was undertaken at Baragwanath Hospital and extended over 3 years (1966–1969), when 370 consecutive cases were examined and treated. A detailed report of this study is to be published elsewhere. One of the major findings was that the prognosis was directly related to the size of the hyphaema (Table I). The problem of management thus mainly concerns the three-quarters to full hyphaemas, since, in our experience, those occupying half the volume of the anterior chamber or less have a good prognosis irrespective of the type of treatment and even with no treatment at all.

Table I *Traumatic hyphaema treated according to size*

Size	*Less than half of volume of anterior chamber*		*More than half of volume of anterior chamber*	
	No.	*Per cent.*	*No.*	*Per cent.*
No. of cases	213		157	
Raised intraocular pressure	8	3·8	133	84·7
Incidence of complications	47	22·0	123	78·3
Final vision of 6/18 or better	166	78·0	44	28·0

This paper reports our experience with the use of Urokinase as a fibrinolytic agent in twenty cases of full hyphaema, associated with large blood clots in the anterior chamber, which could not be washed out with saline.

There have been many reports of the use of fibrinolytic substances†, but these dealt with only eight cases or less, with no attempt to compare the results with those of other forms of treatment. None of the patients had previously been treated by anterior chamber washout with saline.

Materials and methods

In the early part of the study before Urokinase was available, the effect of conservative as against surgical management was investigated, 98 cases selected at random were treated conservatively‡ and 59 cases by immediate anterior chamber wash-out with saline through a small corneal incision.

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*Rychener (1944), Laughlin (1948), Thyeson and Beard (1952), Duke-Elder (1954), Sorsby (1964), MacDonald (1964), Oksala (1967) Darr and Passmore (1967)

†Pierse and Le Grice (1963, 1964), Scheie, Ashley, and Burns (1963), Heath (1966)

‡Conservative treatment comprised rest in bed, pad to the injured eye, topical antibiotic

SURGICAL TECHNIQUE

Incision

This was made with a von Graefe knife through the peripheral part of the cornea, 1–2 mm. in front of the limbus. The incision was slanted within the corneal stroma so that suturing was unnecessary, and was extended to about 15°. The posterior lip of the incision was depressed with an iris repositor to evacuate the fluid blood from the anterior chamber.

Irrigation

Saline from a 2 ml. syringe with a blunt cannula was then introduced into the anterior chamber through the incision; care was taken to keep the tip of the cannula just within the incision and directed away from both the corneal endothelium and the lens capsule, *i.e.* over the iris and parallel to it. The anterior chamber was then gently irrigated with saline until it was free of blood.

UROKINASE

This was used in twenty cases in which anterior chamber wash-out with saline had failed to evacuate large blood clots. In eight cases, the patients were returned to the ward after anterior chamber irrigation with saline and were assessed the following day. They were then subjected to a second anterior chamber wash-out with Urokinase through the same incision. In the other twelve cases, Urokinase was used at the first operation after irrigation with saline had failed to remove blood clot.

The Urokinase was supplied fresh in ampoules by Leo Laboratories as a lyophilized powder and used soon after delivery. If some delay before use is anticipated, the Urokinase should be stored in a refrigerator. 5,000 units Urokinase solution was made up by mixing the powder with 2-ml. sterile distilled water. The anterior chamber was irrigated slowly, with 0·3 ml. Urokinase solution and this was left *in situ* for 3 minutes and then washed out with saline. This procedure was repeated five times. With each introduction of Urokinase the clot became more friable and easier to disperse. If any residual clot was present at the end, 0·3 ml. Urokinase was left in the anterior chamber for 24–48 hours. This caused no harmful effects, and every small clot which remained in the anterior chamber after operation had dissolved completely within 48 hours.

Results

These were assessed by the following criteria in the twenty cases in which saline irrigation was unsuccessful:

(1) Rate of dispersal of blood from the anterior chamber;

(2) Incidence of complications of the hyphaema;

(3) Final visual acuity.

(1) *Rate of dispersal of blood*

In the eight patients in whom Urokinase was used on the next day, it was found that the blood clot had remained the same size and that the intraocular pressure was elevated.

With the use of Urokinase, the blood clot absorbed completely on the operating table in four cases.

In a further four cases it had dissolved before the first post-operative dressing on the first day, and in five more cases within 3 days.

Only two cases took longer than 1 week to absorb completely (one in 7 days and one on the 9th postoperative day), and it was felt that in these cases a higher concentration of Urokinase was necessary to dissolve the blood clot. This was achieved by using 10,000 units (2 ampoules) dissolved in 2 ml. sterile distilled water. In one case, in which 5,000 units Urokinase had had no effect, immediate irrigation with 10,000 units succeeded in dissolving the clot completely.

A comparison between the group of full hyphaemas treated conservatively, those irrigated with saline alone, and those irrigated with saline plus Urokinase shows that the rate of absorption of blood from the anterior chamber (Figure) was slowest in the first group, more rapid in the second, and markedly accelerated in the last.

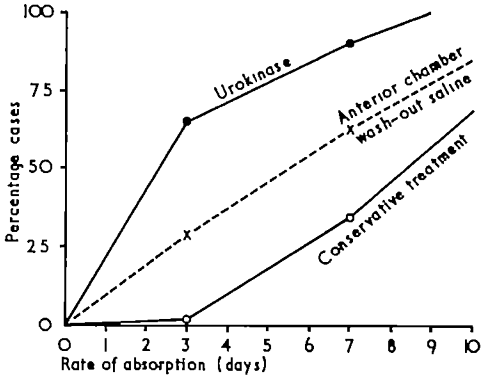

FIGURE *Rate of absorption of blood from anterior chamber*

With conservative treatment only 35 per cent. of hyphaemas had absorbed within 1 week, whereas with saline irrigation 62 per cent. and with Urokinase irrigation 90 per cent. had absorbed completely within 1 week.

(2) *Incidence of complications*

The incidence of major complications before treatment (Table II) was least in the group treated conservatively, greater in the group treated with saline washout, and highest in the group treated with Urokinase.

Table II *Incidence of major complications before and after treatment*

Treatment		*Conservative*		*Anterior chamber irrigation*			
				With saline		*With saline plus Urokinase*	
		No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*
Corneal blood staining	Before treatment	27	27·6	29	49·2	2	60
	After treatment	21	21·6	10	16·9	2	10
Raised intraocular pressure	Before treatment	85	85·8	56	94·9	20	100
	After treatment	49	49·7	12	20·3	1	5
Clotting in anterior chamber	Before treatment	19	19·6	29	49·2	20	100
Fibrous membrane formation	After treatment	33	33·7	21	37·9	2	10
Total cases		98		59		20	

The effect of the type of treatment in reducing the incidence of complications is seen most markedly in the group treated with Urokinase (where blood staining of the cornea was reduced from 60 per cent. before treatment to 10 per cent. after treatment, raised intraocular pressure from 100 to 5 per cent., and fibrous membrane formation occurred in only two cases (10 per cent.) although all the cases in this group had large anterior chamber blood clots). The reduction of complications was also marked, although less so, in the group treated with saline, and least in the group treated conservatively. In fact, from a 20 per cent. incidence of blood clotting in the anterior chamber at the start of treatment, fibrous membrane formation occurred in 33·7 per cent. of these cases; blood clotting must have occurred while these patients were receiving conservative treatment.

The relative incidence of minor complications in the three groups is essentially similar (Table III).

Table III *Incidence of minor complications*

Treatment	*Conservative*		*Anterior chamber irrigation*			
			With saline		*With saline plus Urokinase*	
	No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*
Pigment on endothelium	15	15·5	10	16·9	3	15
Pigment on lens capsule	10	10·5	6	10·2	2	10
Pigment on vitreous	3	3·3	3	5·1	2	10
Posterior synechiae	15	15·5	11	18·6	2	10
Peripheral anterior synechiae	2	2·2	0		0	
Cholesterol crystals	3	3·3	0		0	
Total cases	98		59		20	

(3) *Final visual acuity (Table IV)*

The final visual acuity is poor in all three groups, irrespective of the type of treatment. The acuity recorded is that observed on discharge. As such, it is partly related to the presence of associated ocular injuries which depend on the severity of the initial injury rather than on the type of treatment. Their presence is often not diagnosed until the hyphaema has absorbed and their treatment is of necessity delayed.

Table IV *Final visual acuity*

Treatment	*Conservative*		*Anterior chamber irrigation*			
			With saline		*With saline plus Urokinase*	
	No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*
6/18 or better	33	33·7	11	18·9	4	20
6/24 to 6/60	11	11·2	11	18·9	5	25
Less than 6/60	54	55·1	37	62·2	11	55
Total cases	98		59		20	

The associated ocular injuries were essentially the same in all three groups (Table V, overleaf) and this may explain the similarity in visual acuity.

There is a high incidence of vitreous haemorrhage and traumatic cataract in full hyphaemas, and it may thus be difficult to assess the underlying retina and choroid, so that the incidence of retinal oedema, retinal tears, retinal detachment, and choroidal tears is probably much higher than is shown here. These two injuries are mainly responsible

Table V *Associated ocular injuries*

Treatment	*Conservative*		*Anterior chamber irrigation*			
			With saline		*With saline plus Urokinase*	
	No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*
Vitreous haemorrhage	50	50	30	51	9	45
Traumatic cataract	26	26	22	37	10	50
Dislocated lens	6	6	4	7	2	10
Traumatic iritis	24	24	9	15	2	10
Iris sphincter tears	6	6	1	1·7	1	5
Iridodialysis	4	4	0		1	5
Angle contusion	21	21	17	28	5	25
Retinal oedema	3	3	2	3·4	2	10
Retinal tears	5	5	2	3·4	2	10
Retinal detachment	1	1	2	3·4	2	10
Choroidal tears	1	1	0		0	
No injury	28	28	4	6·7	1	5
Total cases	98		59		20	

for the poor visual acuity. In the group treated conservatively there is a significantly higher incidence of traumatic iritis than in the other two groups.

Discussion

Early surgery is important in the management of full hyphaemas (Rakusin and Kuming, 1969). Factors against continued conservative treatment include:

(1) The slow rate of absorption.

(2) The small effect on lowering the incidence of complications—in fact the results suggest that clotting had occurred while patients were actually receiving conservative treatment.

(3) The high incidence of traumatic iritis.

With traumatic hyphaemas which occupy more than three-quarters of the volume of the anterior chamber, two clinical types are recognizable, one in which the blood is mainly fluid and one in which it is clotted. In the first type blood is easily washed out with saline, but in our experience, only 45 per cent. of cases of the second type can be easily treated with saline alone. In large hyphaemas irrigation with saline succeeded in increasing the rate of absorption and decreasing the incidence of complications, but two disturbing features were noted:

(1) A high incidence (36 per cent.) of fibrous membrane formation. This presumably occurred as a result of organization of clots which could not be evacuated with saline.

(2) In many cases (38 per cent.) the clot took longer than 1 week to absorb.

Obviously saline irrigation alone is often inadequate and fibrinolysis is required to dissolve the blood clot.

The ability of urine to dissolve a thrombus had long been recognized, but the active principle, Urokinase, was first isolated and purified by Ploug and Kjeldgaard (1957). This protein of human origin is entirely non-antigenic. It is a plasminogen activator and converts plasminogen to plasmin which digests fibrin. In the twenty cases in which Urokinase was used, it markedly increased the rate of absorption of blood from the anterior chamber and decreased the incidence of complications.

The results in patients treated conservatively and those treated with saline irrigation can be compared, but, it is not strictly accurate to include the group treated with Urokinase. These patients formed a highly selected group of the most severely traumatized eyes (in which there was a 100 per cent. incidence of large blood clot formation in the anterior chamber and of raised intraocular pressure and a 60 per cent. incidence of corneal blood staining) in whom saline irrigation had failed. They form a group, in fact, acting as its own control, since in each patient saline was used unsuccessfully before Urokinase. They compare very favourably with the other groups, in which the trauma was less severe (as suggested by the lower incidence of glaucoma, corneal blood staining, and blood clot formation before treatment was started).

We feel that Urokinase has a significant role in the management of large traumatic hyphaema associated with large anterior chamber blood clots, and urge that it should be readily available in the operating theatre when saline irrigation is to be performed, so that it may be used immediately in difficult cases, so avoiding the need for a second surgical operation.

Our suggested schedule for the management of large traumatic hyphaemas is shown in Table VI.

Table VI *Management of three-quarters to full hyphaema*

(1) *Conservative treatment*
Should *not* be continued for longer than 48 hours without definite improvement (*i.e.* I.O.P. normal and blood absorbing).

(2) *Surgery*
(*A*) *Anterior chamber irrigation with saline*
Good response—when blood remains fluid
—in 45 per cent. of clotted hyphaemas

(*B*) *Anterior chamber irrigation with saline plus Urokinase*
Immediately after washout with saline in cases in which blood clot remains in anterior chamber

Summary

In twenty patients who sustained traumatic hyphaemas occupying the whole of the anterior chamber together with large blood clots unsuccessful irrigation of the anterior chamber with saline was followed by the use of Urokinase. There was an increased rate of absorption and fewer complications than in two groups of similar hyphaemas treated conservatively or by irrigation with saline alone.

Early irrigation with saline should be performed in cases of traumatic hyphaemas occupying more than three-quarters of the volume of the anterior chamber, and Urokinase should be available for immediate use if saline alone is ineffective.

I wish to thank Leo Laboratories for their assistance and for supplying the Urokinase, and the Medical Superintendents of the Baragwanath and St. John Eye Hospitals for permission to publish these case records. Financial assistance for the study was provided by the University of Witwatersrand, the Medical Research Council, and the C.S.I.R.

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Fluorescein fundus photography of angioid streaks

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The most characteristic ocular lesions in pseudoxanthoma elasticum are the angioid streaks which may be seen in about 85 per cent. of cases. The associated features in the fundus are a peculiar mottled appearance (Shimizu, 1961), *peau d'orange* (Smith, Gass, and Justice, 1964), and yellowish-white spots (salmon spots). While most subjects showing angioid streaks have pseudoxanthoma elasticum, clinically and histologically indistinguishable angioid streaks are also seen in Paget's disease (osteitis deformans) (Shaffer, Copelan, and Beerman, 1957), and sometimes in sickle cell disease (Paton, 1959; Geeraets and Guerry, 1960), familial hyperphosphataemia (McPhaul and Engel, 1961), idiopathic thrombocytopenic purpura (Yatzkan, 1957), and lead poisoning.

The histopathological appearances of angioid streaks have been described by Hagedoorn (1939), Klien (1947), and Verhoeff (1948). Bruch's membrane takes up intense basophilic staining and shows evidence of deposition of metal salts such as calcium or iron. The membrane shows peripapillary cracks with radial extensions. Initially there is a thinning of the pigment epithelium. Later fibrovascular tissues from the choroid invade the retina. The underlying choroid capillaries undergo degeneration.

Many fluorescein fundus photographic studies have been made in cases of angioid streaks (Norton, Gass, Smith, Curtin, David, and Justice, 1965; Ernest and Krill, 1966; Tanenbaum and de Margerie, 1966; Rosen, 1968; Wessing and von Noorden, 1958). There is a broad agreement on the fluorescein pattern, but the interpretation of the fluorescence phenomenon is neither uniform nor satisfactory.

Present investigations

Three cases of angioid streaks have been studied by fluorescein angiography, and one of these, a case of pseudoxanthoma elasticum showing a complete picture of angioid streaks and associated features in the retina, is reported below.

Case report

A man aged 32 years with a histologically proven diagnosis of pseudoxanthoma elasticum was referred* for investigation of defective vision. The skin over the neck showed the characteristic changes of the condition (Fig. 1, overleaf). The visual acuity was 6/24 in the right eye and 6/12 in the left, not improved by glasses. Both fundi showed typical angioid streaks extending radially

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*By a dermatologist, Dr. D. N. Mullay

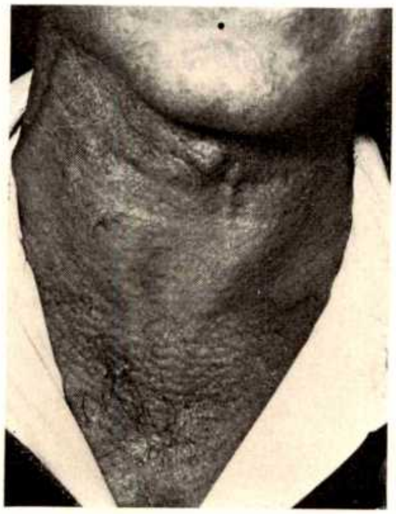

FIG. 1 *Typical skin lesions on the neck*

round the disc (Fig. 2A). The macula was traversed by the streaks on each side. The temporal periphery showed diffuse pigmentary mottling. In the left eye yellowish-white (salmon) spots were seen in bunches along the radiating streaks (Fig. 3A). There were also many isolated spots in both fundi. The electroretinogram was normal in both eyes.

Serial fluorescein fundus photography of the left eye was carried out by the technique of Novotny and Alvis (1961).

Comments

Fluorescence along the streaks was seen during the early arterial phase. Though the fluorescein pattern was sharply defined, it did not conform to the outline of the angioid streaks as seen with the ophthalmoscope (Fig. 2A, B, opposite). The early fluorescence was almost certainly a window phenomenon, *i.e.* the choroidal fluorescence was seen through the defects in the pigment epithelium which normally mask it.

Within seconds the fluorescent zone spread out with an ill-defined outline. The spreading fluorescein (Fig. 2D) obscured the nonfluorescent dark islets inside the fluorescent zone seen in the earlier phases (Fig. 2B, C). Rosen (1968) interpreted this phenomenon as a staining of the sclera. Tanenbaum and de Margerie (1966) considered it as an intravascular pooling of the dye rather than as an extravasation of dye in the choroid. However, any fluorescence on the choroidal side of the pigment epithelium should have the same outline as that of the window in the pigment epithelium, and this spread can only be seen if the dye spreads out on the retinal side of the pigment epithelium.

The evidence suggests that the unbound fluorescein passes readily through the choriocapillaris (Hill, Dollery, Hodge, and Scott, 1964; Hill, 1966; Wessing and von Noorden, 1958). It appears that this extravasated dye finds its way through the ruptured Bruch's membrane and the defects in the pigment epithelium and spreads out in front of this layer. In advanced cases with fibrovascular ingrowth from the choroid, the fluorescein on the retinal side of pigment epithelium could also originate from these new formed vessels. Persistence of fluorescence could be due to the retention of dye in the retina in proliferated tissue from the choroid, and in the sclera.

The fluorescein pattern in the region of the salmon spots (Fig. 3, overleaf) was of four types:

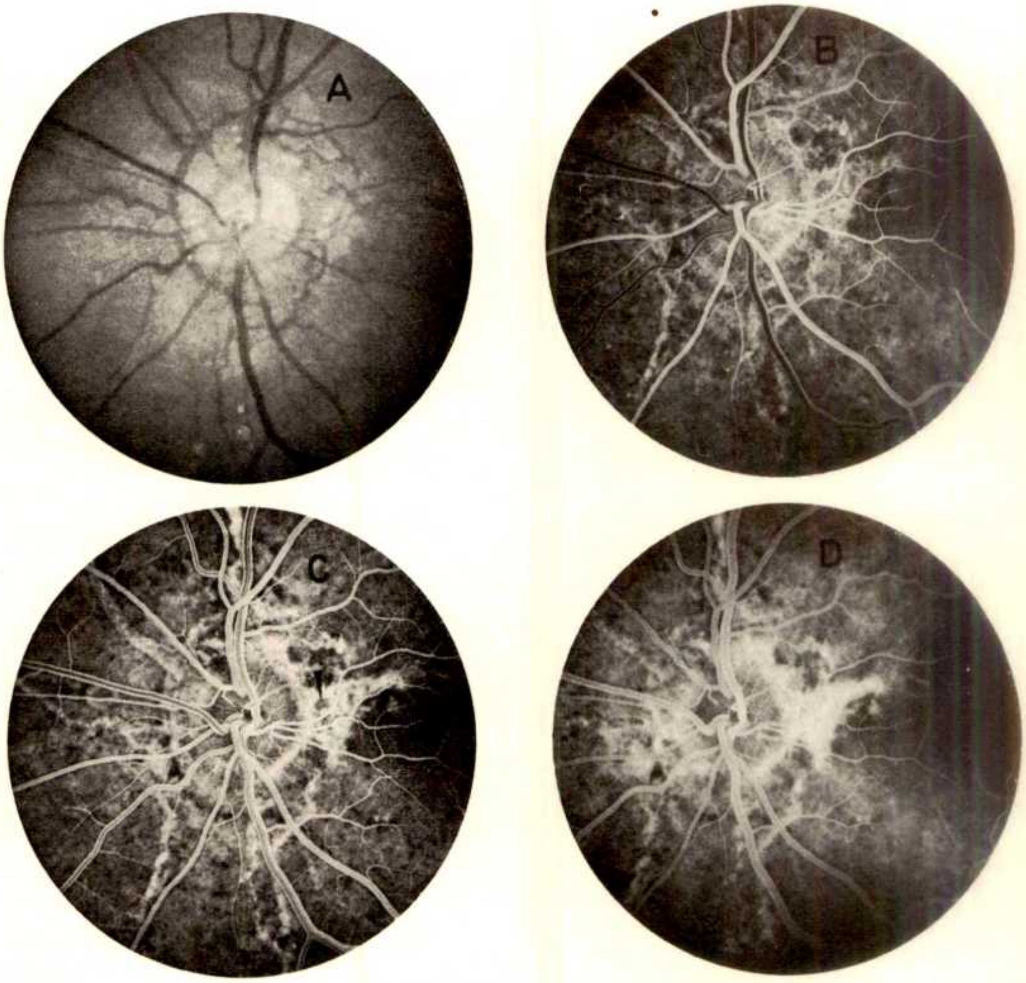

FIG. 2 (A) *Left fundus, showing angioid streaks round the disc. A few of the many salmon spots are seen at the 6 o'clock position*

(B) *Fluorescein photograph at early venous phase. Fluorescence is seen along and not so much over the angioid streaks*

(C) *2 sec. later there is increased density of fluoresecnce. The outlines of the fluorescent areas are fuzzy. Islets of poor fluorescence are surrounded by dense areas (arrow)*

(D) *8 sec. later there is marked diffusion of the dye, specially round the disc. The nonfluorescent islets are swamped by leaking fluorescein*

(*i*) A part of the area occupied by a bunch of salmon spots showed no fluorescence.

(*ii*) The area of fluorescence conformed to the size of the spots.

(*iii*) The fluorescence developed as a coherent background pattern independent of the salmon spots. They could not be identified in the fluorescein photographs.

(*iv*) The area of fluorescence was larger than that of the spots.

The position of the spots could be made out by a faint pigment ring corresponding to the outline of the spots.

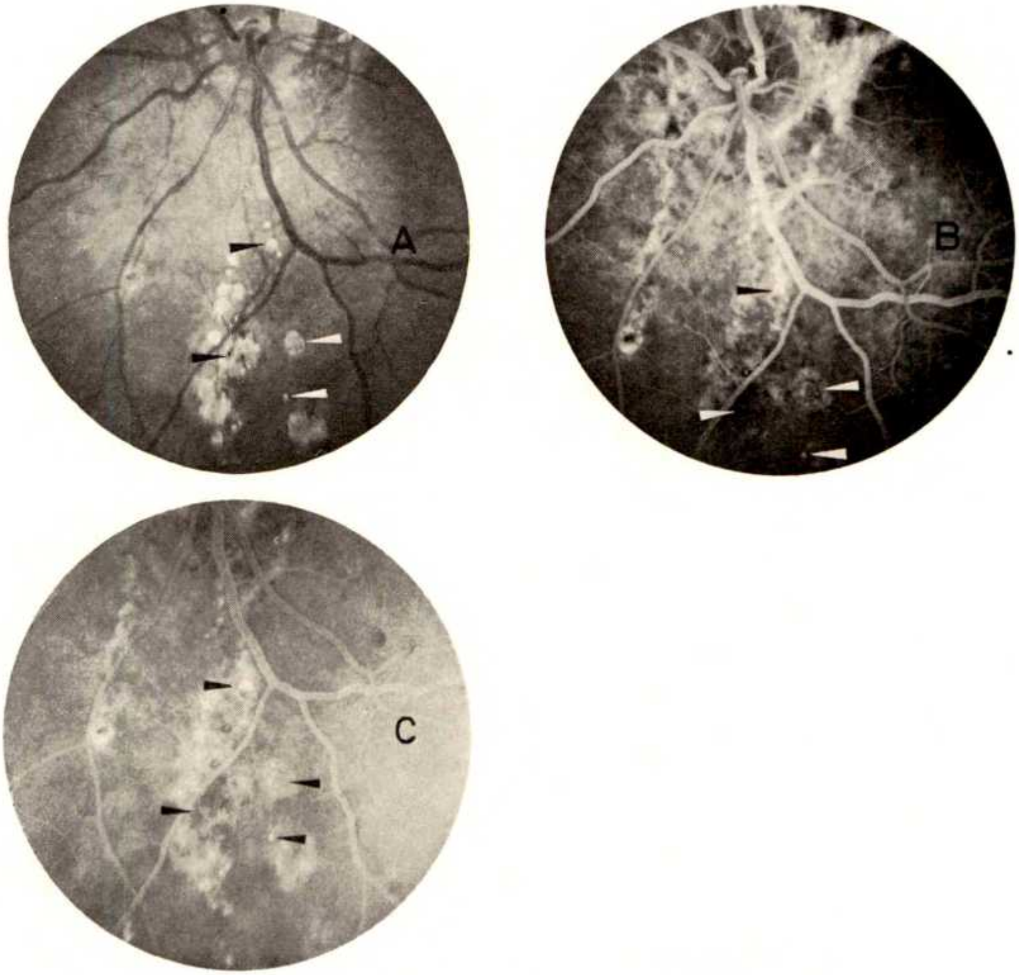

FIG. 3 (A) *Left fundus, showing multiple salmon spots and streaks in discrete or confluent bunches*

(B) *Fluorescein photograph in arterio-venous phase on 2nd injection about 3 min. after the first. Some of the salmon spots showed no fluorescence (arrow: bottom left). A small spot (arrow: bottom right) has assumed fluorescence of equal size. The fluorescence has developed as a coherent pattern in the background, where the identity of the salmon spots is lost (arrow: top left). Though the area of fluorescence is larger than the salmon spot, its outline can be made out (arrow top right)*

(C) 15 *min. after injection. Fluorescence of salmon spots as in* (B). *The reduced contrast is due to fluorescence in the anterior chamber*

From these observations the following conclusions may be drawn. The spots were situated in areas showing widespread disturbances in the pigment epithelium and Bruch's membrane. The appearance of the spots in the fluorescein photographs seemed to depend on the change in the underlying pigment epithelium. If the pigment epithelium did not permit choroidal free fluorescein to reach the spots, they remained nonfluorescent (Type 1). On the other hand, if there was a leakage, the spots took up the dye. When the area of leakage conformed to the size of the spots, they retained their outline as fluorescent spots (Type 2). However, if the leakage in the surrounding area was marked, the contrast was lost and the fluorescent spots lost their identity (Type 3). It appears that the spots are occasionally associated with a pigment pattern corresponding to the size of the spots; when the dye leakage was mild this pigment pattern could be made out (Type 4).

The possibility of pseudofluorescence or autofluorescence of the salmon spots may be excluded, because a group of these spots (Type 1) remained nonfluorescent throughout the study, although their white refractile appearance was ophthalmoscopically identical with that of other salmon spots (Types 2 and 3) showing different degree of fluorescence (Fig. 3).

Histopathology suggests that these spots are hyaline deposits in the form of colloid bodies. Norton, Smith, Curtin, and Justice (1964) believed that drusen did not take up fluorescein, but Rubinstein and Paton (1966) maintained that they did. Drusen of the disc has been found to be fluorescent on fluorescein angiography (Sanders and ffytche, 1967). Thus it would appear that, when exposed to extravasated free fluorescein, the hyaline bodies take up fluorescein and retain it for over 15 minutes.

Summary

A case of pseudoxanthoma elasticum with angioid streaks was examined by fluorescein fundus photography. The pattern of fluorescence around the salmon spots is described. An attempt has been made to interpret the behaviour of fluorescein in the presence of angioid streaks.

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Corneal optical prostheses

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Recent advances in the field of plastic optical corneal prostheses suggest that they have finally moved from the experimental to the clinical field. To some extent this feeling is justified because in the past 10 years many types of keratoprostheses have been used, improving vision in eyes which would otherwise have remained blind. The numerous publications on this subject and the various models and modification of existing prostheses indicate that the ideal corneal prosthesis has not yet been found and that this search continues (see Bibliography).

The main problem with these devices continues to be that of extrusion, which in our limited but varied experience occurs with any type of prosthesis. The purpose of this paper is to report our experience with the Cardona prostheses and the Girard model, and to bring attention to a previously unrecognized cause of extrusion, that of rejection of the homografted tissue used as tectonic material.

Report of cases and results

Altogether 21 prosthokeratoprostheses of three types were implanted (to July, 1970).

(1) Six implants with a fenestrated interlamellar plate (Cardona) also called the "through-and-through";

(2) Five acrylic implants with dacron mesh interlamellar plate (Cardona and Girard-Fig. 1);

(3) Ten "optico-cosmetic" implants (Cardona–Fig. 2).

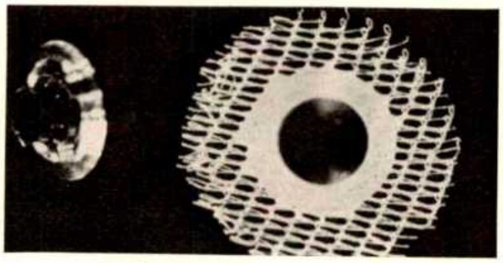

FIG. 1 *Cardona 2·3 mm. "through-and-through" prosthesis, and Girard 3·5 mm. dacron mesh prosthesis*

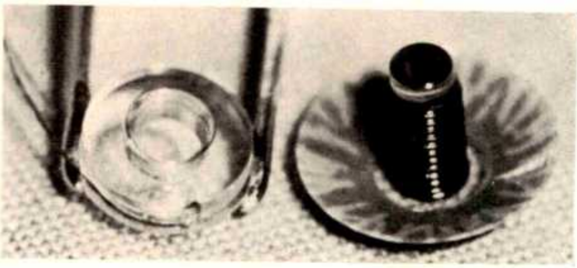

FIG. 2 *Cardona optico-cosmetic keratoprosthesis, also called "nut-and-bolt"*

The results in each case are shown in the Table, opposite.

(1) The first type of Cardona implant was placed in two corneae with repeated failed grafts for bullous keratopathy, one opaque vascular cornea, and three eyes with previous failed grafts for chemical burns. One prosthesis was replaced by the mesh type implant

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Table *Results in three groups of cases*

Type of prosthesis	*Case no.*	*Visual acuity**		*Size (mm.)*	*Time (mths)*		*Condition*
		Degree	*Whether improved*		*Extruded*	*Retained*	
Cardona all-acrylic	1	20/200	Yes		4	Re op. Case 5a	Failed grafts
	2	20/400	Yes		30	—	Chemical burn
	3	20/100	Yes		—	24	Failed grafts
	4	Counting fingers	Yes		—	18	Scar, vascularization
	5	Perception of light	No		24	Re op. Case 3b	Chemical burn
	6	Hand movements	Yes		32	32 Reop. Case 10b Re op. Case 10b.	Chemical burn
Acrylic mesh	1a	Counting fingers	Yes	3·5	—	30	Lye burn
	2a	20/400	Yes	4	5	—	Failed grafts
	3a	Hand movements	No	4	4	—	Failed grafts
	4a	20/400	Yes	4	(conjunctival flap)	24	Lye burn
	5a	20/400	Yes	2·3	—	18	Failed grafts. Extruded prosthesis. Rejected grafts
Optico-cosmetic	1b	20/400	Yes		—	13	Lye burn
	2b	Perception of light	No		5 (rejected graft)	—	Lye burn
	3b	Hand movements	No		—	6	(Failed graft previous-prosthesis)
	4b	Counting fingers	Yes		12	—	Chemical burn
	5b	20/80	Yes		3 (necrosis)	—	(Advanced bullae scarring vascularization)
	6b	Perception of light	No		10	10	Failed grafts
	7b	Counting fingers	Yes		—	12	Failed grafts
	8b	Counting fingers	Yes		—	16	Lye burn
	9b	20/50	Yes		—	14	Alkali burn
	10b	Perception of light	No		1 (infection)	—	(Lye burn. Previous prosthesis)

*In every case the preoperative visual acuity was perception of light

when a large corneal erosion developed around the cylinder 4 months later. Two were extruded at 2 and 2½ years respectively and were replaced by an optico-cosmetic implant. The other three implants have been retained for 2 years or more with minimal central erosion (Figs 3 and 4).

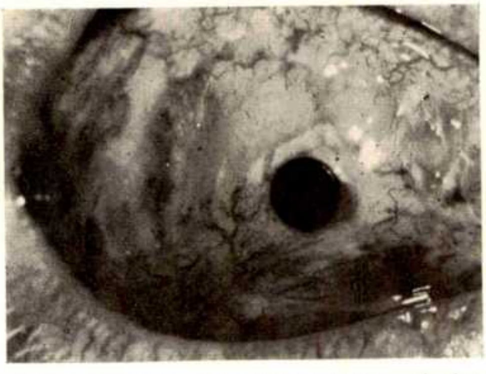


FIG. 3 *Cardona all-acrylic prosthesis with three fenestrations in a cornea with a failed transplant. It has now been in place for over 2 years*

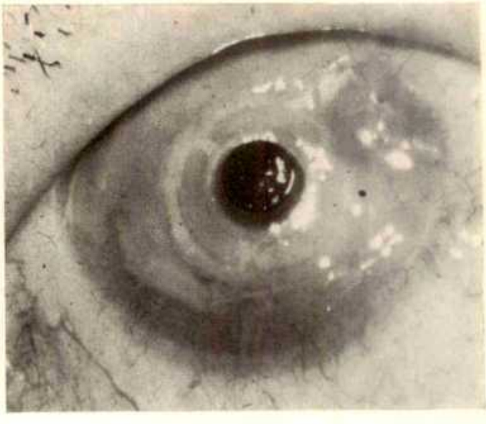


FIG. 4 *A similar type of Cardona keratoprosthesis which has been in place for 2 years*

(2) Three of the five mesh type prostheses are still retained after 1½ years. Two were extruded at 4 and 5 months respectively, because of necrosis of the sclera in one case and rejection of scleral graft in another. The impending extrusion of Case 4a was treated successfully with a conjunctival flap and has now been retained for over 2 years. (Fig. 5).

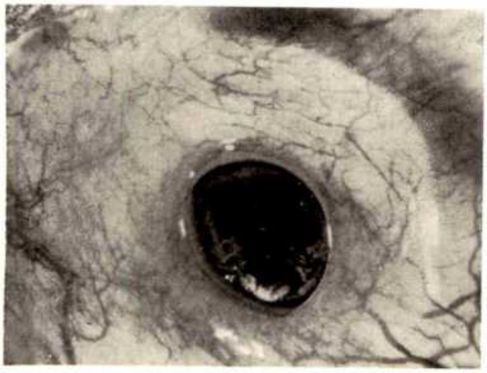


FIG. 5 *4 mm. mesh keratoprosthesis which has been in place for over 2½ years in an eye with lye burns. A conjunctival flap covers part of the prosthesis and there is an intermittent leakage of aqueous humour*

(3) Six of the ten optico-cosmetic prostheses have now been in place for up to 1½ years, and two of these show tissue loss around the cylinder.

Burns with lye or ammonia were the original cause of injury in eleven of 21 cases. Three of these ("through-and-through" model) extruded the implant after 2 years. This is a good tolerance period if one compares them to three cases with repeated graft failure

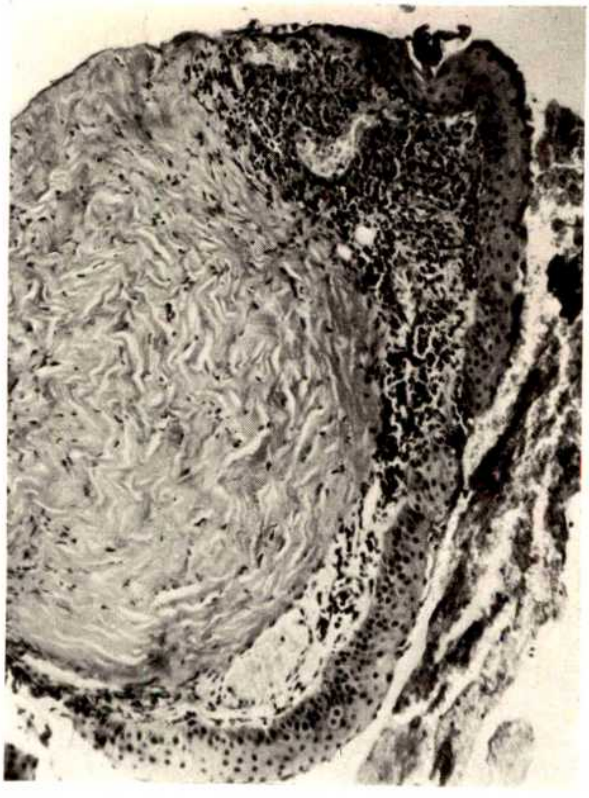
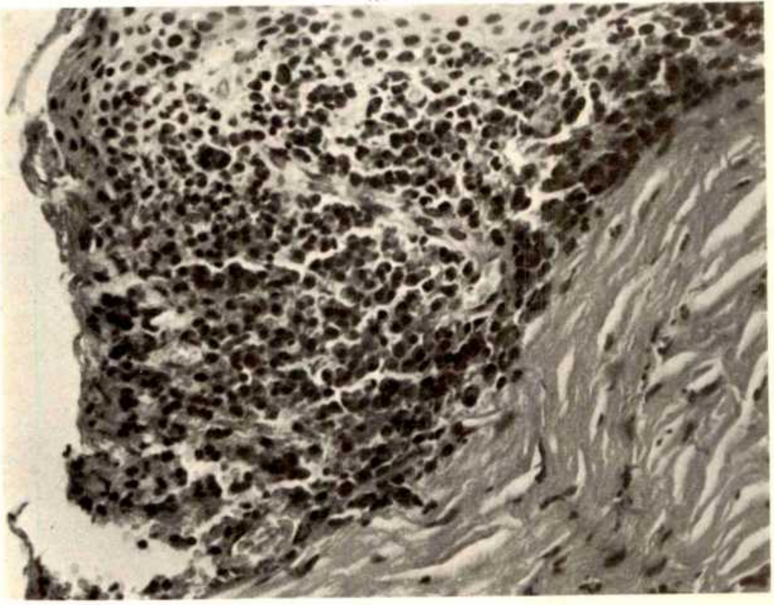


FIG. 6 *Epithelialization of the corneal perforation in an eye with an optico-cosmetic prosthesis—a round cell inflammatory reaction is present in the anterior portion of the cornea. Haematoxylin and eosin.* ×80

which extruded at 4 and 5 months. Extrusion in two eyes with a failed graft with lye burns, and in one with a scleral homograft, seemed to have been caused by rejection of the homograft into which the prosthesis was placed, with epithelium advancing into the anterior chamber throught the corneal fenestration in one case (Figs 6 and 7). In another extrusion of an optico-cosmetic implant and in a cornea with a "through-and-through" prosthesis, epithelium also advanced to the anterior chamber (Fig. 8).

(7)



(8)

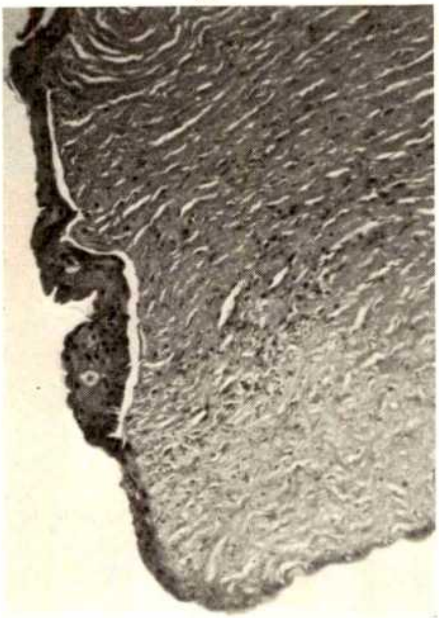


FIG. 7 *Higher magnification of area of inflammation and tissue destruction shown in Fig. 6. Lymphocytes and plasma cells form the infiltrate where there is destruction of corneal lamellae. Haematoxylin and eosin.* ×160

FIG. 8 *Growth of corneal epithelium along the corneal fenestration into the anterior chamber. Haematoxylin and eosin.* ×78

Comment

Even though the tolerance of plastic implants in the cornea is limited, its use is indicated in eyes with multiple graft failures and particularly in corneae with chemical burns. Most of our patients with chemical burns are now fitted with the Cardona optico-cosmetic prosthesis on a corneal transplant; the follow-up period for these implants is short when compared to the earlier "through-and through" model. Some of the objectionable complications inherent to the first models mentioned were solved with the cosmetic prothesis, but we feel that reoperations are easier and complications less severe with the former implants.

Epithelial downgrowth is one of the risks of this procedure and may develop with any of the prostheses used, including the implant with rigid interlamellar plate. Infection is another possibility but is fortunately not common; it occurred in one patient shortly after the implantation of an optico-cosmetic prosthesis when he left the country for 2 weeks without medical approval.

Early and late complications are present with all implants (Girard, Moore, Soper, anp O'Bannon, 1969; Castroviejo, Cardona, and DeVoe, 1969). Erosion of tissue around the prosthesis is probably the most common complication. It may occur as "melting" of the cornea in interlamellar implants, loosening of optico-cosmetic implants through necrosis, or destruction of homografted tissue by an immune reaction. This phenomenon may occur with corneal or scleral grafts and its recognition may permit the eye to be treated with steroids and so to avoid extrusion. Scleral necrosis due to poor conjunctival covering is another possibility and is difficult to treat once the scleral graft has started to disintegrate.

If an implant can be replaced by a corneal graft or by a new one when extrusion is imminent, a tolerance of 2 to 3 years is a good average in eyes with chemical burns. Tolerance may be higher in eyes with bullous keratopathy, but we feel that these eyes deserve one or more grafts before a prosthesis is implanted. The extrusion rate in large series of cases with random corneal diseases varies from 11 per cent. in a 4-year follow-up (Girard Wong, Lempert, Moore, Soper, and O'Bannon, 1969) and 10 per cent. in an 8-year follow-up (Cardona, Castroviejo, and DeVoe, 1967), to 20 per cent. in a 10-year follow up (Castroviejo and others, 1969). Therefore, the prognosis is not so poor if one considers that this is the only procedure available for eyes which carry the worst visual prognosis (Cardona, Castroviejo, and DeVoe, 1963).

Most of these eyes have previous retinal disease and glaucoma, two conditions which account for the poor visual results in these series and often make the assignment of numerical visual results irrelevant. However, in one case of lye burn with an optico-cosmetic prosthesis, a vision for distance of 20/50 was obtained with a hydrophilic lens over the prosthesis. It is possible that glaucoma, if present, may be controlled by aqueous leakage around the prosthesis as it could be observed in one case which has had a built-in fistula for over 3 years (Fig. 5). It is our impression that the all-acrylic "through-and-through" prosthesis offers a better insurance against epithelial downgrowth when placed in an interlamellar situation even though this complication may still occur.

Another complication observed with all prostheses is the formation of a fibroblastic membrane behind the prosthesis or a pre-vitreal membrane which causes a decrease in visual acuity. Sectioning or excision of the latter is not always successful. Retinal detachment was suspected in two cases and was observed in one through a 4 mm. prosthesis 4 months after implantation. It was not possible, however, to obtain good visualization for surgery.

Because of the eventual extrusion of the implants and the number of potential complications, this is necessarily an experimental procedure open to modifications and improvements.

Summary

Three types of keratoprosthesis were implanted in 21 eyes. Eleven cases had a history of alkali burns, and most of the eyes had retained a prosthesis for 2 years or more. Several frequent complications include necrosis of the recipient tissue around the implant, epithelial downgrowth, and infection. Rejection of tectonic corneal or scleral homograft (often used as part of the procedure) is another complication not previously recognized.

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Proptosis as a manifestation of acute myeloid leukaemia

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Orbital or subconjunctival infiltration occurs frequently in acute and chronic lymphatic leukaemia, but only rarely in myelogenous leukaemia (Chatterjee and Sen, 1960). Chloroma, an atypical form of myeloblastic leukaemia, often manifests itself as a localized mass in the orbital periosteum, and the proptosis produced in such cases may be the first sign of the disease (Goodman and Iverson, 1946). It is estimated that two-thirds of patients with myeloid leukaemia present with some blurring of vision and accompanying fundus changes.

Although orbital infiltration in myelogenous leukaemia certainly occurs (Consul, Kulshrestha, and Mehortra, 1967; Crombie, 1967; Reese and Guy, 1933; Mortada, 1963; Gupta, Agarwal, and Pratab, 1970; Mathur, Gupta, Nema, and Katiyar, 1970), it is not a frequent manifestation, and the two cases reported below are therefore of interest.

Case reports

Case 1, a girl aged 7 years, was brought to JIPMER Hospital with a 15-day history of gradual and painless but progressive bilateral proptosis. There was no history of trauma, facial sepsis, or of any bleeding disorder or epistaxis.

GENERAL EXAMINATION

The patient was restless, looked ill, and was markedly anaemic. The pulse rate was 90/min. and the temperature 99°F. The cervical lymph nodes were not palpable. There was no oedema over the mastoid region and no evidence of sternal tenderness. The cardiovascular and respiratory systems were normal. The liver and spleen, which were just palpable, were smooth and soft.

OCULAR EXAMINATION (Fig. I, opposite)

Both eye lids were swollen and tense. The conjunctiva was markedly chemotic and congested. There was an irreducible axial proptosis. The globe was immobile in all directions. There was evidence of the corneae, with a hypopyon ulcer on the right cornea while the left was hazy and lustreless. Details of the posterior segment could not be seen.

DIAGNOSIS

Leukaemia with bilateral proptosis. Other possibilities were bilateral orbital cellulitis, cavernous sinus thrombosis, and neuroblastoma, with orbital deposits.

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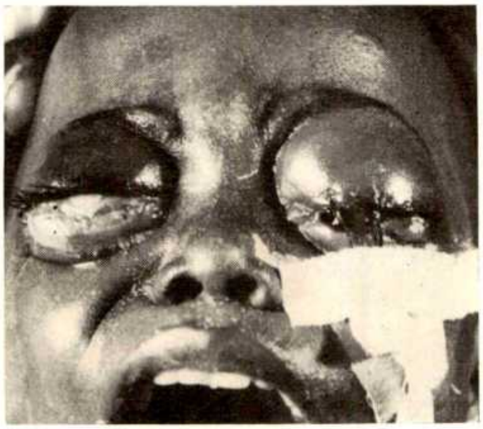
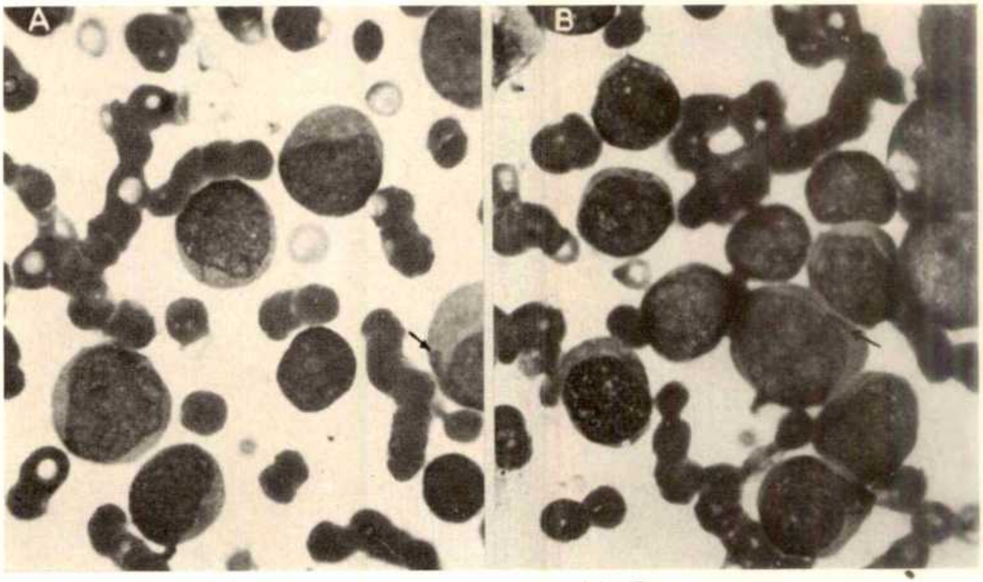


FIG. 1 *Bilateral proptosis due to acute myelogenous leukaemia (Case 1)*

LABORATORY INVESTIGATIONS

The urine and stools were normal. Hb 8g./100 ml.

Total white blood cells 70,000 per cu. mm.; neutrophils 12 per cent., eosinophils 2 per cent., lymphocytes 2 per cent. The peripheral blood film (Fig. 2A) showed myeloblasts 68 per cent., promyelocytes 5 per cent., and myelocytes 7 per cent.



(A) *Peripheral blood smear* × 100 (B) *Bone marrow smear* × 100

FIG. 2 *A group of myeloblasts, one showing Auer bodies (arrow)*

The bone marrow film (Fig. 2B) showed hypercellularity with marked depression of erythropoiesis and megakaryocytopoiesis. There was marked proliferation of myleoid cells with a large number of myeloblasts and promelocytes. Erythroid/myeloid ratio 1/60. Plasma cells 0·1 per cent.

Serum iron 83 μg. per cent. and serum uric acid 7·3 mg. per cent.

Chest *x* ray was normal. *X* ray of the orbits showed soft tissue shadows on both sides. The maxillary antra were hazy.

TREATMENT

The diagnosis of acute myeloid leukaemia with secondary orbital deposits leading to proptosis was confirmed, and the patient was given oral prednisolone 5 mg. 6-hrly with terramycin syrup and supportive therapy. Local treatment aimed to prevent exposure of the corneae, and a temporary lid suture was placed on the left side. Local antibiotics and atropine ointment were instilled.

Case 2, a 3-year-old boy, was brought to the hospital with a history of prominence of the left eye and mild intermittent fever for one week. There was no accompanying pain in the eye and no history of local trauma. No swellings has appeared elsewhere in the body.

EXAMINATION

The child did not appear to be ill. No lymphadenopathy was observed. The liver and spleen were not palpable.

OCULAR EXAMINATION

The right eye was normal. The left eye showed axial proptosis with gross limitation of all ocular movements (Fig. 3). The proptosis was not significantly reducible. There was partial dropping of the lid. No conjunctival chemosis was present. The cornea was clear and the pupil showed sluggish reaction to light. Ophthalmoscopy revealed normal fundi.

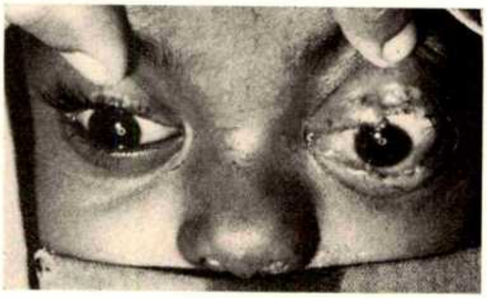


FIG. 3 *Proptosis of left eye due to acute leukaemia* (*Case* 2)

LABORATORY INVESTIGATIONS

Nothing abnormal was found. *X* rays of the optic foramen and orbits were normal.

PROGRESS

A week after admission, the proptosis had slightly increased with conjunctival chemosis in the lower part. The fundus showed early papilloedema with a few haemorrhages. Slight exposure keratitis developed on the lower part of the cornea and a median tarsorrhaphy was done.

An epistaxis 10 days after admission led us to investigate the case for a bleeding disorder, with the following results:

Total white blood cells 7,900/cu.mm., bleeding time 5 min.; clotting time 3 min.; erythrocyte sedimentation rate 100 mm./1st hr (Westergren). The peripheral blood film showed myeloblasts 14 per cent., promyelocytes 2 per cent., metamyelocytes 1 per cent., neutrophils 16 per cent., and lymphocytes 67 per cent.

Bone marrow biopsy showed normal cellularity. Erythropoiesis showed normoblastic depression. There was marked myeloid hyperplasia. Some promyelocytes and myeloblasts were seen. Erythroid/myeloid ratio 1/12. Plasma cells 0·2 per cent.

DIAGNOSIS

Myeloid leukaemia.

TREATMENT

The child was given oral prednisolone 5 mg. 6-hrly with intravenous injections of Endoxan 100 mg. biweekly, with supportive therapy.

RESULT

The patient responded favourably after 3 weeks; the proptosis was reduced with return of ocular movements.

Discussion

Proptosis in cases of leukaemia may be caused by retrobulbar haemorrhage or leukaemic deposits in the orbital cavity. Leukaemic proptosis may not always be accompanied by marked leucocytosis and premature cells in the peripheral blood smear as observed in Case 2. In such cases the diagnosis of leukaemia may be missed unless a bone marrow biopsy is performed as a routine investigation in all cases of proptosis in children (Crombie 1967), especially those of sudden onset. The incidence of proptosis in cases of lymphatic leukaemia has been reported as 2 per cent. (Reese and Guy, 1933), but it is rare in myeloid leukaemia.

Chloroma, a variant of acute myeloid leukaemia, commonly produces proptosis as a result of subperiosteal orbital infiltration (Sorsby, 1951). Whatever the nature and colour of the deposits the incidence of chloroma is fast declining.

The proptosis in cases of leukaemia tends to be bilateral with associated conjunctival chemosis (Case 1), but there was unilateral proptosis in Case 2. A sudden onset of bilateral proptosis in a child should suggest the conditions of bilateral orbital cellulitis, cavernous sinus thrombosis, acute leukaemia, or neuroblastoma with secondary orbital deposits. In the first two conditions there is usually an obvious focus of sepsis around the head and face and the patient is very toxic. Bilateral orbital cellulitis is uncommon. Neuroblastoma can be ruled out by examination for abdominal tumour. An examination of the peripheral blood film and bone marrow will reveal the presence of leukaemia.

Summary

Two cases of acute myeloid leukaemia presented with proptosis, one bilateral and one unilateral. The diagnostic difficulties are discussed.

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Bilateral oedema at the posterior pole

Hypersensitivity reaction to Alavac P injection

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Many diseases affecting the eyes are considered to be allergic manifestations (Cooke, 1947), but the retina and optic nerve are involved only rarely; retinitis, detachment of the retina, and optic neuritis may result (Tassmann, 1946).

A contrary view is that retinal oedema was common during the era of serum therapy because of the high incidence of serum sickness. Foods, pollens, and drugs were also frequently incriminated (Boyd and Aaron, 1963).

In the following case, bilateral macular oedema occurred as a hypersensitivity reaction to densitizing pollen vaccine.

Case report

A man aged 26 years first attended on April 2, 1970, complaining of poor vision in both eyes. The visual acuity in the right eye had deteriorated 10 days previously, followed 2 days later by the left eye; this was associated with metamorphopsia, micropsia, defective depth perception, and positive central scotomata. Initially, the general symptomology was headache, neck stiffness, and extreme lethargy. On the day of onset of the ocular symptoms, he had received an injection of Alavac P (Bencard), which had been prescribed for hay fever and respiratory allergy beginning at the age of 22 years. This was his second annual course, and he was receiving no other medical treatment. There was no history of trauma, pre-existing visual disability, or family history of allergy.

EXAMINATION

The visual acuity was 6/36 and N18 in both eyes. Skiascopy + 4·0 D sph. both eyes. There was no improvement in distance or reading vision with the addition of a plus lens. The pupils were equal and regular with reaction to light and near reflexes. Fundus examination revealed an ill-defined raised greyish area, involving both posterior poles, with mottling at the maculae, and loss of the foveal reflex. The optic disc and retinal blood vessels were normal, retinal haemorrhages and exudates were absent, and the vitreous was clear. Both visual fields charted on the Bjerrum screen showed an absolute central scotoma to white targets (2/2000 and 5/2000).

The patient was admitted to hospital.

INVESTIGATIONS

X rays of the skull and chest, lumbar puncture, and blood studies showed no deviation from normal values.

PROGRESS

On April 2, treatment with oral prednisolone 10 mg. 8-hrly was started. On April 4, the visual acuity in the right eye was 6/12, and in the left eye 6/9. The macular oedema had practically subsided. On April 7, the visual acuity was 6/5 in both eyes. The fundus appearances were normal

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except for slight mottling at the maculae. Reduction in steroid dosage was begun. On April 28, he had no complaints, the visual acuity was 6/4 in both eyes, the macula appeared normal, and the visual fields charted on Bjerrum's screen showed no residual relative or absolute scotomata.

Comment

Necheles (1964) described a case of spontaneous recurrent macular oedema. An episode then occurred after a desensitizing vaccine injection given 24 hours previously. Further episodes occurred when the injection was repeated. The vaccine consisted of extracts of ragwood, grasses, tree pollens, and airborne moulds. Retinal oedema of allergic origin, following the injection of antitetanus serum, was suggested by Bedell (1935). Williams (1933) incriminated pork-insulin and Wiener (1935) suggested tricophyton as allergens causing retinal oedema.

The features of interest in the case described above are the rapid response to prednisolone, the full recovery of visual function, and the absence of eosinophilia. Earlier injections of Alavac P resulted in a gradual increase in local tissue antibodies, *i.e.* the induction of a state of tissue hypersensitivity.

Lesions of the retina due to oedema, haemorrhage, or inflammation may be postulated as allergic in origin but proof is difficult to substantiate. Cooke (1947) stated that, if "some" of the following criteria applied, there was evidence of allergy in the aetiology of the clinical condition:

(1) History of antecedent allergy.
(2) History of other allergies in the patient.
(3) History of recurrent attacks not explained on any other medical basis.
(4) Blood eosinophilia not due to intestinal parasites.
(5) Well-marked skin tests.

It is suggested that the present case belongs to the category of an allergic reaction. The risk of retinal oedema after desensitizing vaccines is rare and there is no reason to cease this form of prophylaxis, but the continuation of injections in an affected patient is not recommended.

Summary

A case is described of bilateral posterior polar oedema due to hypersensitivity to Alavac P. This is the second recorded case of retinal allergy to desensitizing vaccine. The criteria for evidence of an allergic aetiology are stated.

I wish to thank Mrs. J. Hudson for her help in the preparation of this paper.

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Lymphocyte transformation test in sympathetic ophthalmitis and the Vogt-Koyanagi-Harada syndrome

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The lymphocyte transformation test (LTT) has been shown to be a reliable method of demonstrating the antigen of delayed-type allergic responses. The test is based upon the process of gradual enlargement, transformation into lymphoblasts, and mitotic activity of small mature lymphocytes in the peripheral blood which occurs when they come into contact with an antigen to which the organism has previously been sensitized (Pearman, Lycette, and Fitzgerald, 1963; Marshall and Roberts, 1963; Daniels, Ritzmann, and Levin, 1968; Ling, 1968). The mechanism of this blastic transformation appears to be identical with that of lymphocyte activation observed in the course of homograft rejection. Blastogenesis will not take place if no antigen has been added to the lymphocyte cultures, or if the donor organism has not been previously sensitized to the antigen tested.

Phytohaemagglutinin (PHA) is known to stimulate aspecifically the blastic transformation of lymphocytes cultured from healthy subjects (Hungerford, Donelly, Nowell, and Back, 1959; Nowell, 1960), but this stimulation does not occur if the subject suffers from a disease damaging the immune apparatus or is receiving immunosuppressive treatment (Daniels and others, 1968; Bozsóky, 1969).

In this paper the effects of uveal pigment and PHA on lymphocyte cultures from patients with sympathetic ophthalmitis (SO) or the Vogt-Koyanagi-Harada syndrome (VKHS) are compared.

Methods

LYMPHOCYTE CULTURES

These were taken from two patients suffering from the VKHS and three with SO. Cultures from five ophthalmologically healthy subjects served as controls. Diagnosis was based on the histories and typical clinical signs as well as the histological findings.

ANTIGENS

Uveal pigment not containing soluble proteins prepared from bovine eyes according to the method of Woods (1925) was used for specific stimulation. Phytohaemagglutinin M (0·01 U/ml.) manufactured by Difco was used for aspecific transformation.

CULTIVATION OF LYMPHOCYTES

Lymphocytes isolated from citrated venous blood by sedimentation were cultured in a 5-fold volume of Parker 199 solution (Simon, Dobozy, and Hunyadi, 1969). The lymphocytes were not separated

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from the other leucocytes during the experiments. The stimulating compounds were added at the start of cultivation, in 0·1 ml. volume per culture. At least three 3-ml. cultures were secured from each subject; the first was stimulated with appropriately diluted uveal pigment, the second with PHA, and the third, used as control, with isotonic saline.

After cultivation for 4 days, 3μ Ci H^3-thymidine was added in 0·1 ml. volume to each culture and cultivation was continued for an additional period of 24 hours. On the fifth day, 5 per cent. trichloracetic acid was added to the cultures to precipitate the macromolecules, and acid-soluble thymidine was removed by washing three times in trichloracetic acid. The scintillation counts of the DNA-containing sediment were established by means of a Tri-Carb apparatus (Packard).

The rate of stimulation was estimated from the increment of H^3-thymidine incorporation, a manifestation of the increased synthesis of DNA during blast transformation. The extent of blast transformation was assessed from the ratio of scintillation-counts in stimulated and non-stimulated cultures; the LTT was considered to be positive if this index was higher than 1·5.

Results

The concentration of uveal pigment eliciting the highest degree of blast transformation was determined first. Lymphocyte cultures from one patient with SO and from another with the VHKS were stimulated with different concentrations of the antigen. The incorporation of H^3-thymidine was highest at a final concentration of 2 μg/ml. uveal pigment. Higher and lower concentrations resulted in lower transformation indices (Table I). Uveal pigment was used at 2 μg/ml. level in all subsequent experiments.

Table I *Determination of optimal stimulating dose of uveal pigment*

Concentration of uveal pigment (μg./ml.)	*Quotient of scintillation counts (index) in cultures stimulated and not stimulated by uveal pigment*	
	VKHS	*SO*
200·0	1·4	1·2
20·0	1·9	2·1
2·0	2·3	2·6
0·2	2·0	1·8
0·02	1·3	1·4

Table II *Blast transformation stimulating effects of uveal pigment and PHA in lymphocyte cultures obtained from patients and healthy controls*

Patient no.	*Diagnosis*	*Uveal pigment*	*PHA*
1	VKHS	1·7	9·2
2		2·9	5·3
3	SO	2·1	6·7
4		1·6	8·8
5		2·4	5·0
6	Control	1·1	8·9
7		0·8	7·3
8		1·0	3·9
9		1·2	12·5
10		0·9	5·6

The figures represent quotients (indices) of scintillation counts in cultures stimulated and non-stimulated

The specific transformation elicited by uveal pigment yielded more than 1·5-fold increase of H^3-thymidine incorporation into the lymphocyte cultures of all patients suffering from SO or the VKHS. The same antigen failed to stimulate the lymphocyte cultures of the ophthalmologically healthy subjects. Blast transformation evoked by PHA was of much greater degree than that due to the specific antigen, but was of about the same magnitude in cultures from patients and healthy subjects (Table II).

Discussion

Elschnig (1910) and Woods and Little (1933) were the first to postulate the antigenic role of pigment in the pathogenesis of SO. This idea was supported by Friedenwald (1934), who compared the tissue-reaction after the intracutaneous administration of uveal pigment to the features of SO (Friedenwald, 1934); this is now interpreted as a delayed-type allergic response to the pigment. McPherson and Woods (1948) obtained identical results in the VKHS and SO with the uveal pigment skin-test. Kahán and Sztanojevits (1964) observed a correlation between the results of the skin-test and the activity of the above diseases. Uveal pigment agglutinating antibodies were demonstrated in the sera of patients suffering from the VKHS or SO if the combining antibodies were completed by Coombs-serum (Kahán, Sztanojevits, Szabados, Vass, and Szabó, 1964).

In the present experiments, the lymphocyte cultures of all patients with SO or the VKHS could be stimulated by uveal pigment, but the pigment consistently failed to enhance the incorporation of H^3-thymidine into cultures from healthy subjects.

These findings suggest that the uveal pigment has a specific transforming action upon the lymphocytes in these diseases. As most authors agree upon the reliability of the LTT in confirming delayed hypersensitivity, it is concluded that autoaggressive cell-bound responses to the pigment may play a role in the pathogenesis of both SO and the VKHS.

Summary

Lymphocyte cultures from two patients with histologically confirmed Vogt-Koyanagi-Harada syndrome and from three patients with sympathetic ophthalmitis were stimulated with bovine uveal pigment. The best antigen concentration was 2 µg/ml., which increased the blast transformation 1·6 to 2·9 times, as assessed by the incorporation of H^3-thymidine. The uveal pigment failed to stimulate the lymphocyte cultures from healthy subjects. The specific transforming action of uveal pigment indicates that these diseases are of a pigment autoaggressive delayed allergic nature.

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Chorio-retinal hazards in aphakia

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We are taught—though it is impossible to establish on what authority—that the human crystalline lens specifically protects the retina and choroid from thermal damage. To be more precise: if a glass blower has had a lens removed because of a radiation cataract he is advised not to return to his job. It seems, however, that, if his vision can be restored to enable him to resolve all the necessary detail, and suitable heat absorbing spectacles are prescribed and worn, this advice is ill-founded.

Other things being equal, the unaided aphakic but otherwise normal human eye produces an image with 1·24 linear magnification as compared with the normal phakic eye (Emsley, 1952). It is, therefore, more than 50 per cent. larger in area than is true of the corresponding phakic eye. Hence the radiation flux density on the retina of the aphakic eye is less than two-thirds of the normal, or, at the chorio-retinal level, the normal eye is exposed to a 50 per cent. larger hazard than exists for the aphakic case.

The volume absorption of the crystalline lens is replaced by that of the aqueous and vitreous humours and/or kindred aqueous fluids. In the infra-red part of the spectrum, which is associated with heat, the absorption of the phakic eye behaves as though the whole of the pre-retinal media were aqueous (Aschkinass, 1895; Lenoble and Le Grand, 1953).

Consequently such filtering protection as the crystalline lens affords is confined to the visible and ultra-violet parts of the spectrum. It is this absorption which has to be made up by a suitable yellow filter (Verriest, 1963; Said and Weale, 1959). In addition, the glass blower or furnace attendant, or any other person whose eyes are exposed to a nearby high-temperature source, must, of course, wear the protective shield or goggles issued to workers whose eyes are intact. There should be no significant drop in visual performance. In fine, given that the aphakic worker can see as well as is necessary for his job, and that he is provided both with light filters which compensate for the absorptivity of the crystalline lens in the visible and the ultra-violet parts of the spectrum and also with the normal light shield, there is no obvious reason why he should not return to his job as soon after an operation for a thermal cataract as is feasible.

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Ocular effects of antifreeze poisoning

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Human poisoning by antifreeze mixture has been known for many years and its formula, $HOC\ H_2$—CH_2OH, occupies a position between ethyl alcohol and glycerol. Mostly it has been drunk by mistake, but sometimes it has been ingested as a substitute for alcohol (Ross, 1956).

The minimum lethal dose was regarded by Hunt (1932), as 100 ml., but complete recovery after drinking 250 ml, has been reported by Kahn and Brotchner (1950). Brain, lungs, liver, and the kidneys are the main organs affected by systemic intoxication and renal failure is the usual cause of death. There is no specific antidote. Treatment is as for oxalate poisoning, because ethylene glycol is metabolized to oxalic acid which is deposited in various organs as calcium oxalate crystals.

Few ophthalmological cases have been reported. Sykowski (1951) described the topical effects of ethylene glycol on the human eye, chemosis, keratitis, and acute iridocyclitis with dust-like keratic precipitates and exudate in the anterior chamber being the main features.

Friedman, Greenberg, Merrill, and Dammin (1962) reported four cases of antifreeze poisoning. Two patients, each 17 years of age, had ingested 3 to 4 oz. of ethylene glycol. Dilated pupils with loss of light reflexes and bilateral papilloedema were noted in one patient, who died 47 hours after ingestion of the mixture. The other patient, who developed bilateral ophthalmoplegia and blurring of the optic discs, died on the 17th day. Those who drank 1–2 oz. had no eye lesions and recovered completely.

Case report

A 58-year-old man drank about half a pint of antifreeze mixture in divided doses over a period of 48 hours. He claimed that he had mistaken it for whisky, but the fact that he drank it in repeated small quantities shows that it could not have been accidental.

About 16 hours after the last drink he noticed great difficulty in seeing; he became extremely depressed and was admitted to hospital for psychiatric care.

EXAMINATION

14.3.69 The patient was depressed but conscious and co-operative. The pupils were dilated and nonreactive to light. There was no perception of light in either eye. The optic discs were of normal colour.

15.3.69 The optic discs became blurred.

18.3.69 The pupils reacted sluggishly to light and near reflex. Visual acuity was hand movements in the right eye and counting fingers at 30 cm. in the left. The optic discs were blurred.

31.3.69 The pupils were normal, and the visual acuity was counting fingers at 1 m. in each eye. Temporal pallor of the optic discs was developing.

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1.4.69 The visual acuity had recovered to 3/60 in the right eye and 2/60 in the left. The discs were pale and the patient was unable to recognize blue, green, and red.

21.5.69 Visual acuity 6/18 in the right eye and 4/60 in the left. Colour vision was still defective.

20.8.69 The visual acuity had deteriorated to 4/60 in the right eye and counting fingers in the left. There was marked bilateral optic atrophy. No further improvement occurred.

Summary

A case is described in which bilateral optic atrophy developed as a consequence of drinking antifreeze mixture.

I wish to thank Dr. M. Rusk and Dr. W. Wilson for their advice in the preparation of this paper.

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Injury to the eye by the sap of *Euphorbia royleana*

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The saps of some plants are known to be highly irritant to the eye. We have recently seen a patient in whom accidental splashing with the sap of *Euphorbia royleana* caused acute bilateral conjunctivitis with corneal ulceration and iridocyclitis. *Euphorbia royleana* (Churee) is used as a hedge in some parts of India to protect crops from predatory or stray animals. It is a glabrous fleshy shrub of cactus-like aspect, and is common on hills below 6,000 ft. in the Western Himalayas (Figs 1 and 2). The thick white milky sap contains alkaloids (Collett, 1902).

Case report

A man aged 36 years came to the H.P. Medical College Hospital, on February 24, 1971, with acute pain and soreness of the eyes. He had been cutting branches of the shrub 6 days previously with the object of planting them around a field, when the sap splashed into his eyes. He felt excruciating

(1)

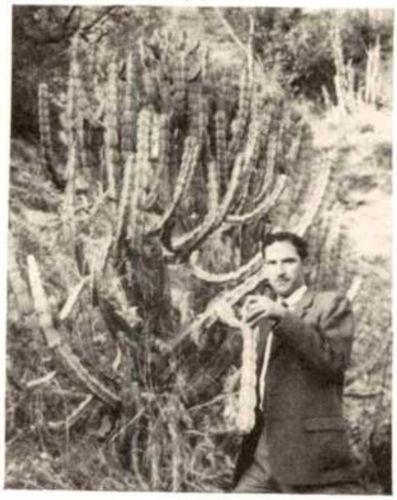

FIG. 1 *The shrub* Euphorbia royleana *compared with the height of a normal man*

(2)

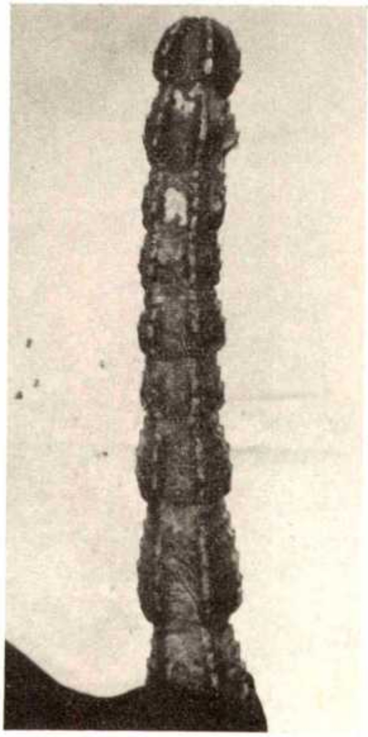

FIG. 2 *A branch of the shrub*

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pain and watering from the eyes and almost complete loss of vision with swelling of the lids. He had no treatment for 24 hours, but then the juice of another plant locally called Nanhuan (*Sedum multicaule*) was instilled into the eyes and gave slight relief. As the pain persisted and vision was seriously impaired he came to the hospital, but not until 6 days after the accident.

EXAMINATION

He was a slim healthy man with normal pulse and respiration. The eyes showed marked photophobia, swollen lids, and chemosed conjunctivae. The corneae were hazy and oedematous and in places ulcerated. The anterior chamber, iris, pupil, lens, and posterior segment could not be seen. The visual acuity was reduced to perception of light.

The patient was admitted to hospital and treated with saline irrigations, atropine 1 per cent., and terramycin eye ointment three times a day, and later with corticosteroid eyedrops. His condition steadily improved and the chemosis regressed.

On March 19, 1971, the chemosis had completely subsided but there was still marked congestion. The corneal ulcers had healed leaving superficial corneal opacities. The pupils were semidilated and irregular with multiple posterior synechiae. The visual acuity was 4/60 in the right eye and 2/60 in the left.

Discussion

The sap of plants of the Euphorbiaceae family are known to cause vesicant dermatitis and chemotic conjunctivitis with keratitis. According to Duke-Elder (1954), Snow and Harley (1944) described ocular complications caused by the sap of the apple beech, and the irritant is believed to be Urushiol or a related compound (Merrill, 1944). Ocular reaction has been reported from the saps of other members of the same family—*Tithymalus cyparissias* (Hilbert, 1897), *Euphorbia antiquorum* (Santos Fernandez, 1892), and *Tithymalus esula* (Lewin and Guillery, 1913).

In our case the sap of *Euphorbia royleana* produced intense conjunctival, corneal and iritic inflammatory reaction, but no dermatitis. The acute reaction may have been due to the greater penetration of the sap alkaloids through the cornea.

Summary

A case is reported of ocular injury resulting from the sap of *Euphorbia royleana*.

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Miotics or mydriatics for atony of the ciliary muscle with delayed re-formation of anterior chamber after cataract extraction with complete iridectomy

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In cases of delayed formation of the anterior chamber after intracapsular extraction of senile cataract, the cause must be searched for:

(1) The incision should be carefully examined for leakage, a procedure aided by the instillation of fluorescein. If there is a leak the ocular tension will be low. A tiny subconjunctival leak may be difficult to diagnose.

(2) The fundus must be examined for the presence of choroidal detachment, a condition also accompanied by hypotony.

(3) The eye must be examined with the slit-lamp for pupillary block by vitreous. Chandler (1954) described four types of pupillary block:
A ring synechia of the pupil to an intact vitreous face;
A plug of vitreous occluding the pupillary aperture or any iridectomy that may be present;
The formation of a pupillary membrane;
Blocking by vitreous of a gap in the pupillary membrane after an extracapsular extraction.

In such cases the ocular tension is usually raised and the condition may be treated by mydriatics or complete iridectomy and air injection into the anterior chamber.

In all the above three instances the iris diaphragm is in contact with the posterior surface of the cornea with a risk of peripheral anterior synechiae and secondary glaucoma.

The three conditions (wound leak, choroidal detachment, and pupillary block) may form a vicious circle. A leaking wound, lowering the ocular pressure, may favour dilatation of the choroidal vessels, giving suprachoroidal exudation and detachment of the choroid, and the latter will push the vitreous forwards giving rise to vitreous pupillary block. Choroidal vascular engorgement may push the vitreous forwards increasing the pressure in the anterior chamber on the healing wound, giving rise to a wound leak and loss of the anterior chamber.

In the following 100 cases of intracapsular extraction of senile cataract using the multiple-methods technique (Mortada, 1963, 1965), all the causes of delayed formation of the anterior chamber were prophylactically treated, preoperatively, operatively, and postoperatively. Even so in four cases the re-formation of the anterior chamber was delayed for 4 days without clinical evidence of a leaking wound, choroidal detachment, or pupillary block The effect of miotics and mydriatics on the quickness of re-formation on the anterior chamber was studied.

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Prophylactic preoperative, operative, and postoperative treatment for non-formation of the anterior chamber after cataract extraction was as follows:

(A) PREOPERATIVE PROPHYLACTIC TREATMENT

(1) Improving the general condition of the patient by diet, vitamins, and treatment of hypertension, albumin in the urine, or diabetes.

(2) Treatment of any cause of strain such as cough or constipation.

(3) Use of hypnotics, tranquillizers, sedatives, and anti-histaminics before operation up to the tolerated dose. This helps to prevent uveal vascular engorgement.

(4) Reduction of ocular pressure by acetazolamide (Fine, 1965), or osmotic pressure factors by the use of oral glycerol (Radian, and Radian, 1967), purgatives, or local massage.

(B) OPERATIVE PROPHYLACTIC TREATMENT

(1) The corneo-scleral section must not be irregular or larger than is necessary to get the lens out easily. A von Graefe knife section is better than that done by keratome and scissors (Swan and Campbell, 1946). The best method is a von Graefe knife section on the corneal side of the limbus, 1 mm. above the horizontal meridian on either side with a very small conjunctival flap. This section is best for quick wound healing.

(2) The cautery must not be applied to the lips of the wound.

(3) The three or four conjunctivo-corneo-sclero-conjunctival sutures must be properly placed and equally distributed, using sharp atraumatic needles and virgin silk, and not deeply placed so as to cause necrosis or fistulization. After lens extraction the sutures must not be tied too tightly.

(4) In this series a basal iridectomy was performed to prevent pupillary block by vitreous (Chandler, 1961; Swan, 1963).

(5) The iris must be properly reposited at the end of the operation. No vitreous or lens capsule tissue must be left in the wound in case of complications.

(6) Gauze and cotton threads must not be left between the lips of the wound. Care must be taken not to leave subconjunctival tissue in the lips of the wound after saline irrigation or air injection into the anterior chamber.

(7) Alpha-chymotrypsin must be used only when indicated and must be followed by immediate washing of the wound lips (Kuchle, 1962; Hughes, 1965).

(8) Air must be injected to reform the anterior chamber at the end of the operation. If air does not enter the anterior chamber at the end of operation in the presence of a hermetically sealed wound this means that vitreous is pushing the iris forwards against the back of the cornea. This is usually due to engorgement of the uveal vessels, especially the choroidal vessels, or from reduction in ocular pressure. The engorged choroidal vessels may lead to suprachoroidal exudation and choroidal detachment. Also in the rare event of scleral collapse the air may not enter the anterior chamber.

(9) Care must be taken to avoid separation of the ciliary muscle attachment to the scleral spur and injury of the scleral spur by scleral section, severe mechanical zonulotomy, or pulling the scleral lip of the wound outwards with the forceps during the application of the scleral part of the corneo-scleral suture, especially when the sclera is tough or the needle is not sharp. This will avoid suprachoroidal drainage and choroidal detachment.

(C) POSTOPERATIVE PROPHYLACTIC TREATMENT

(1) Prevention of lid spasm that may occur because of a strong orbicularis muscle, retention of lacrimal fluid in the conjunctival sac, dressing by irritant drops or ointment, release of a suture in the conjunctival sac, entrance of a piece of cotton or gauze into the conjunctival sac, or after the removal of sutures.

(2) Lid spasm or general strain presses the anterior chamber evacuating its contents through a small wound leak.

(3) The corneo-scleral sutures must not be removed before the 12th day, especially in old debilitated patients.

In the four cases in which re-formation of the anterior chamber was delayed for 4 days (in spite of all the above precautions and the absence of clinical evidence of wound leak, choroidal detachment, or pupillary vitreous block,) the effect of miotics and mydriatics was tried.

(1) In two cases pilocarpine eye ointment 1 per cent. was applied twice daily, and in both the anterior chamber was formed on the next day.

(2) In other two cases atropine eye ointment 1 per cent. was applied twice daily. In these two cases there was no improvement. The atropine was then replaced by local pilocarpine and eserine ointment twice daily, and the anterior chamber reformed after 3 days.

These observations favour the theory that atony of the ciliary muscle may be a cause of delayed formation of the anterior chamber after cataract extraction. The atony is due to the pressure of the strabismus hook on the ciliary muscle during extraction of the lens, or pulling on the ciliary body during separation of the zonule, or injury of the ciliary muscle insertion to the scleral spur during a badly-performed scleral section or the introduction of a scleral suture.

Summary and conclusions

In 100 cases of intracapsular cataract extraction with complete iridectomy, elaborate precautions were adopted to prevent delayed formation of the anterior chamber through wound leakage, choroidal detachment, or vitreous pupillary block.

In four cases the formation of the anterior chamber was delayed for 4 days. Local miotics favoured quick formation and mydriatics delayed formation, thus supporting the theory that the condition was due to atony of the ciliary muscle caused by the trauma of the operation.

Atony of the ciliary muscle caused closure of the trabecular meshwork impeding aqueous outflow, and stagnation of the choroidal circulation.

These factors suggested that there was a tiny wound leak under the conjunctival flap.

Miotics contract the ciliary muscle, opening the trabecular meshwork and encouraging choroidal circulation. This reduces the relative aqueous tension in the anterior chamber and assists the closure of the leak.

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Correspondence

Impacted Microfilaria in the Lens Capsule

To the Editorial Committee of the **British Journal of Ophthalmology**

SIRS,—I was much interested in the paper by Min Him Tham and I. B. Hall (*Brit. J. Ophthal.*, 1971, **55**, 484), which constitutes a valuable addition to the literature in this field. It is interesting also that, although *Mf. bancrofti* are found in large numbers in the blood, it is distinctly unusual for them to be reported in the anterior chamber, in contrast to *Mf. onchocerca volvulus* which are never found in the bloodstream but are frequent denizens of the anterior chamber.

I am obliged to the authors for their reference to my paper (Choyce, 1964), but regret that I have been slightly misquoted.

They say:

> "In equatorial Africa, it has been reported that there are half a million filarial patients who are blind (Choyce, 1964)".

What I actually said was:

> "The World Health Organization has estimated that there are perhaps as many as half a million onchocercal patients who are blind. You will note the wording of this sentence, because some of us believe that additional factors may be involved in the blindness".

These additional factors have received considerable emphasis in the intervening years. Attention has been drawn, for example, to the importance of food deficiencies and intoxications; *e.g.* Osuntokun (1971) emphasized the frequency of tropical nutritional neuropathy in Nigeria, including a high incidence of optic atrophy and some cases of choroido-retinitis which he attributed to poisoning by cassava. Cassava contains a cyano-genetic glycoside, from which hydrocyanic acid is released on hydrolysis. Other parasitic diseases are now better documented than formerly, together with their effects on the posterior segment, especially toxoplasmosis and loaiasis.

Genetically-determined ophthalmic disorders brought out by in-breeding are also bound to be more frequent in primitive communities (Choyce, 1958).

I think the statement that half a million onchocercal patients are blind still holds good to-day, but how much of the blindness is due to onchocerciasis and how much should be attributed to these other factors mentioned above is a most difficult exercise and I should not care to commit myself at this time.

Yours faithfully,
D. P. CHOYCE

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September 25, 1971

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Book reviews

The Ocular Fundus. By A. NOVER, trans. F. C. BLODI. 2nd ed., 1970. Pp. 175, 144 figs (some col.), tables. Kimpton, London (£6.75)

This is an atlas of common disorders of the fundus, illustrated by very good fundus photographs which are accompanied by a short description in the text. This book is suitable for those commencing ophthalmology although its price will preclude many of them from buying it.

Perspectives in Ophthalmology. Vol. II. Edited by J. E. WINKELMAN and R. A. CRONE. 1970. Pp. 214, figs (1 col.), refs. Excerpta Medica, Amsterdam

This book contains the papers presented at the 1969 Post-graduate Course organized by the Netherlands Ophthalmological Society. The two topics covered are Genetics and Ophthalmology, and Strabismus and Related Problems.

The first section includes several very good review articles on various aspects of ophthalmic genetics, including papers on Rieger's and Peters's syndromes by Alkemade, heterozygous manifestations in various types of tapeto-retinal dystrophy by de Haas, homocystinuria by François, and the transmission of Leber's optic atrophy by van Senus.

The second section deals with various aspects of strabismus and among the eleven papers is one by Gobin on surgical technique, in which he describes his four-muscle surgery, and one by Leuridan and Noordenbos on binocular vision in unilateral aphakia corrected by a contact lens.

This is a well printed and well illustrated book containing a wide range of articles on topics of particular interest at the present time. It can be recommended to ophthalmologists of fellowship standard and above and has the great advantage that it consists of short papers which can be dipped into from time to time.

Surgery of Caustic Injuries of the Eye. (Die chirurgische Behandlung der Ätzverletzungen des Auges) By B. ALBERTH. 1971. Pp. 119, 105 figs (some col.), bibl. Enke, Stuttgart (Bücherei des Augenarztes, No. 57, suppl. to *Klin. Mbl. Augenheilk.*) (DM 28.80)

This booklet deals mainly with the problems of treating severe caustic injuries of the cornea. Less severe injuries require only subconjunctival injections of blood and instillation of a buffer lotion or ethylendiaminetetra-acetic-acid drops. Most of the procedures recommended by the author are generally accepted; as for example, the damping down of the immune reaction between host and donor tissue, preparatory lamellar keratoplasty in extensive corneal destruction, surgical treatment of an existing symblepharon before corneal grafting, and the transposition of Stensen's duct when the afferent tear ways are obliterated. The author considers oral mucous membrane plastic surgery by the method of Denig to be contraindicated. Experiments in rabbits have shown that there is no caustic deposit under the conjunctiva, and the removal of precious conjunctiva is damaging. In cases of fresh caustic injuries of the cornea, grafting is urgent before oedema and subsequent vascularization make their appearance. The author does not discuss the use of a hypertonic agent, *e.g.* the well tolerated 5 per cent. NaCl-lanolin-petrolate ointment, for preventing the threat of oedema. If the invasion of vessels into the cornea has begun it is better to wait for 6 or 7 months before grafting. It is astonishing how often the author has been able to improve apparently hopeless cases. Even in total symblepharon, the conjunctival sac could be replaced by the technique of Puchkovskaya or the extracorneal keratoplasty of Castelli. This is a small book but conveys much valuable information.

First Congress of the International Strabismological Association. Transactions of a Congress held at Acapulco, Mexico, March 1970. Edited by P. FELLS. 1971. Pp. 312, figs, refs. Kimpton, London. (£7)

This book contains the papers presented at the Congress held in Mexico in March, 1970, and consists of papers on three topics: Early Operations for Strabismus; Non-surgical and Surgical Treatment of Exo-deviations; and the Use of Prisms in Pre- and Postoperative Treatment. It also contains several free papers and the Bielschowsky lecture on Current Concepts of Amblyopia by von Noorden.

The subject matter of these papers reflects the great interest now being taken in the theoretical and practical aspects of strabismus and this book is highly recommended to all those interested in this subject.

Year Book of Ophthalmology, 1971. Edited by W. F. HUGHES. 1971. Pp. 383, 98 figs, refs. Year Book Medical Publishers, Chicago

The 1971 Year Book of Ophthalmology maintains the usual excellent standard achieved by its predecessors. All branches of ophthalmology are covered and this is recommended reading for all ophthalmologists in order to keep up to date with current literature.

Notes

Castellino Prize, 1972

The Nicolò Castellino Foundation announces the sixth international Competition as a tribute to the memory of Professor Castellino. A prize of 1,000,000 Italian lire (about £650) is to be given for the best original unpublished work in the field of industrial medicine on a subject to be freely chosen.

The essay may be presented in various languages, including English. Seven copies (signed only with a motto) should be sent before February 20, 1972, to the Secretary of the Fondazione Nicolò Castellino, Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro, via Guidubaldo del Monte 24, Roma 00197, from whom further particulars may be obtained.

European Contact Lens Society

II Scientific Congress, April, 1972

The Second Scientific Congress of the European Contact Lens Society of Ophthalmologists will be held on April 15 and 16, 1972, in Budapest, immediately before the European Ophthalmological Congress.

Ophthalmologists wishing to attend or read papers should write immediately to the Congress Secretary, Dr. Istvan Gyorffy, Budapest VIII, Maria U. 39, Hungary.

New Orleans Academy of Ophthalmology and Rudolph Ellender Medical Foundation

Ophthalmological Courses, April, 1972

The New Orleans Academy of Ophthalmology and the Rudolph Ellender Medical Foundation have coordinated their programmes so that either or both courses can be attended profitably without significant repetition or duplication of material.

The Rudolph Ellender Eye Foundation will hold its meeting on Saturday and Sunday, April 8 and 9, 1972. The main papers will be on instruction in fitting techniques: "hard lenses" on Saturday and "flexible lenses" on Sunday.

The Symposium of the New Orleans Academy of Ophthalmology will hold registration on Sunday, April 9. Lectures, panel discussions on preselected topics, and "round tables" permitting questions from the floor will be held from Monday to Friday, April 10-14. The lectures will include didactic material on all phases of medical contact lens practice and experience and impressions of an experienced panel with flexible lenses. This will be a comprehensive programme. The New Orleans Academy of Ophthalmology guest lecturers will be Drs. Chester J. Black, Jorge N. Buxton, Herbert L. Gould, G. Peter Halberg, Herbert E. Kaufman, Ian Mackie, Perry Rosenthal, and Whitney G. Sampson.

Course in Neuro-Ophthalmology

National Hospital, London, May 3–5, 1972

At a 3-day Neuro-ophthalmological course to be held at the National Hospital, Queen Square, London, on May 3–5, 1972, there will be contributors from the National Hospital, Queen Square, the Institute of Neurology, the Maudsley Hospital, the Institute of Psychiatry, Moorfields Eye Hospital, and the Institute of Ophthalmology, London. There will also be guest speakers from the U.S.A.

For further details write to the Secretary, Department of Neuro-Ophthalmology, The National Hospital, Queen Square, London, WC1N 3BG

Irish Ophthalmological Society

Annual Meeting, Dublin, May 8–10, 1972

The next Annual Meeting of the Irish Ophthalmological Society will take the form of a Joint Meeting with the Dutch Ophthalmological Society and will be held in Dublin on May 8 to 10, 1972. All communications will be in English. Further information may be obtained from: Dr. G. P. Crookes, Honorary Secretary I.O.S., 18 Fitzwilliam Place, Dublin, 2, Ireland.

Obituary

William Arthur Briggs, 1902–1971

W. A. Briggs, who died on August 13, 1971, was educated at Cambridge and St. Bartholomew's Hospital, London, qualifying in medicine in 1926. Shortly thereafter he went to Lincoln where he became interested in ophthalmology and, having taken a diploma in that subject in 1929, he obtained consultant appointments at Lincoln County Hospital and several others in the same region. He led a busy life with a large ophthalmic practice, but retired from hospital work in 1960 owing to the progress of a disabling illness which became an increasing handicap during the later years of his life. He took a very prominent part in the development of ophthalmology in Lincolnshire where he was widely known and respected. He is survived by a wife and two sons.

Corrigendum

In the article on "Conjunctival Swabbing for the Isolation of TRIC Agent" by S. Darougar and B. R. Jones, in the September issue (*Brit. J. Ophthal.*, (1971), 55, no. 9, p. 586, l 18):

For 'at approximately 6 hrs after inoculation' *Read* 'at approximately 60 hrs after inoculation'

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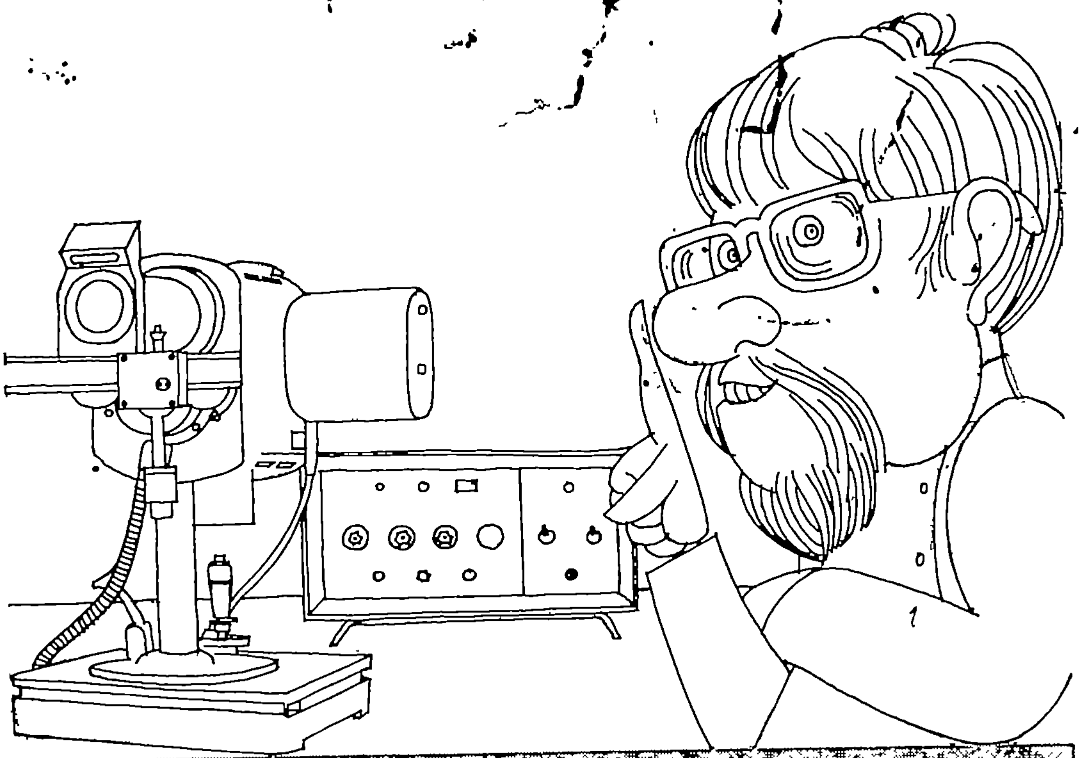

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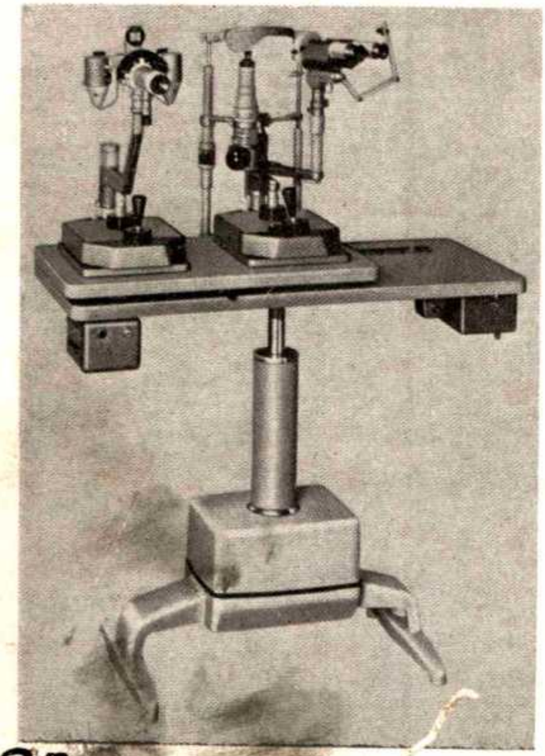

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